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NATIONAL INSTITUTE OF AGING

NATIONAL INSTITUTE ON AGING

Introduction

The average length of life in the United States has increased from 49 to 70 years in this century, due largely to the prevention of early deaths from infectious diseases. Ten percent of the population is now over 65 years of age. The newly established National Institute on Aging (NIA) is responsible for medical, biological, psychological, and social aspects of research relevant to the health of the elderly. The Institute supports research on the multitude of biological changes that occur with aging, studies of cognitive and emotional alterations that occur with increasing age, and investigations of societal aspects of aging. The overall goal is to increase the quality of life in the later years and greatly reduce the costs of health care for the elderly. Research programs are concerned with the development of knowledge that will allow a reduction in the effects of aging processes, particularly those which result in disabilities and fatal diseases by altering function, and will make possible a more productive role for the elderly in our society.

Emphasis Areas in Aging

In the past several decades great progress has been made in detecting and measuring the loss of function, both physiological and psychological, that occurs as humans age. As for reduction in the performance of the body's major systems, much is known, for instance, about the changes that occur in the ability of the kidney to excrete the end products of metabolism, and also about the changes in mental abilities that occur with age. Until recent years, however, little has been known about the responsible underlying mechanisms with which scientists hope eventually to intervene therapeutically. Advances in the biomedical sciences in the last few decades have provided the concepts and tools for studying fundamental aging processes so that in the years to come a complete understanding of aging at a cellular and molecular level will be possible.

The Institute is supporting efforts to develop risk factors (overweight, high blood pressure, smoking habits, etc.) in preventive medicine for the elderly as well as for the general adulthood population. Advances in identification of risk factors in various longitudinal studies are beginning to pave the way toward structuring preventive medical techniques which can make the senior adult years dignified, independent, and productive.

It has recently been discovered that there is a striking diminution in immunological competence with increasing age. The decline is so great that the elderly retain only one-tenth of the peak immune capacity shown during adolescence. Research is being supported to determine whether the immunologic deterioration that occurs with age involves changes in the function of individual cells, changes in the number of specific cells present, or changes in the microenvironment in which they operate. An ability to treat the decline in immunological competence that occurs with age might significantly reduce the incidence of infections, malignancies, and autoimmune diseases in the later years of life.

Many of the metabolic processes carried out by the human body decline with age, and decreases in some of them are detrimental to health. For example, while total caloric consumption decreases with age, many persons tend to become fatter during their middle years. The ability of the human body to maintain low levels of serum lipids decreases with age and the rise in lipids may contribute to the development of atherosclerosis. Research to identify those factors which tend to shift metabolism from protein synthesis to fat synthesis in senior adults will be pursued.

The remarkable decrease in the ability of humans to utilize carbohydrate in the latter half of life raises the question of whether diabetes mellitus becomes more common in humans as they grow older, or whether the observed low tolerance for carbohydrates is different from clinical diabetes. Poor metabolism of carbohydrates is known to lead to vascular disease and other degenerative processes. The Institute will continue to support studies to determine whether the classical treatment for diabetes is indicated in senior adults with low carbohydrate tolerance.

For reasons not yet fully understood, some elderly persons develop disabling memory loss, disorientation and confusion. It appears that a psychologically supportive environment does much to maintain mental function in the elderly, but changes in cellular structure and function in the brain do occur with age. The Institute will support research to determine whether degeneration of mental function is a sequella of chronic desease or a consequence of aging _per se_.

In a number of aspects, aging in women differs from that of men. Women generally live seven to eight years longer than men, and while scientists have postulated that the difference is related to additional genetic material on the X chromosome, to a better immune system, to differences in stress associated with work performed by women, or to hormonal effects, this biologic fact of life remains unexplained. Adjustments that women are called upon to make at certain stages in their lives, such as when the children leave home, or the spouse retires or dies, present special problems for the female. Osteoporosis in old age is physiologic alteration confined primarily to women. Research aimed at elucidating the special problems of aging in women will be undertaken.

A unique event, peculiar to female aging, is the menopause. The phenomenon, initiated unfailingly by an unknown biological clock, indicates cessation of ovulation with accompanying profound psychologic and hormonal changes, and provides a biologic marker for aging. Before menopause women appear relatively protected from age-related degenerative cardiovascular disease and certain other illnesses, compared to men, but afterward, they imitate the male incidence pattern. Research to determine the feasibility, and the desirability, of intervention to modify the biological and behavioral consequences of the menopause, needs to be pursued.

Over the last decade or so, more of the aged have been institutionalized in nursing homes, convalescent homes, and the like. Placement of the elderly in such institutions removes them from a familiar, and often psychologically supportive, social and physical environment. Since the number of elderly so institutionalized is liable to increase because of changing family and societal life styles, increased federal support for health care services, and increasing individual longevity, it is important to know the biological and behavioral effects of institutionalization on the elderly, so that the needs are met of those who must be institutionalized.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

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NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Introduction

Mission of the Institute

The NIAID conducts and supports broadly based research on the causes, characteristics, prevention, control and treatment of a wide variety of diseases believed to be attributable to infectious agents (including bacteria, mycoplasma, fungi, viruses, rickettsia and parasites, such as protozoa, worms and arthropods), to allergies or to other deficiencies or disorders in the responses of the body's immune mechanisms.

Mechanisms for the Support and Conduct of Research

In common with the majority of other NIH institutes the NIAID conducts research in its own laboratories (in Bethesda, Maryland; Hamilton, Montana; and Hawaii) under the aegis of the Intramural Laboratory and Clinical Research Program (frequently nicknamed the Intramural or IM Program). Research is supported by grants to a worldwide net of academic and not-for-profit institutions and laboratories through the Extramural Program (EP). Research training is similarly supported by competitive awards to institutions or individuals, almost exclusively in the United States. Additionally, highly targeted and federally directed research programs are supported by contracts with particularly well qualified academic or commercial institutions worldwide through the Collaborative Research Program (CR).

Although traditionally called Programs; Intramural, Extramural and Collaborative are more appropriately thought of as activities or mechanisms and the word "program" is generally used in this report for a collection or portfolio of related substantive research projects.

Programs

In its attack on infectious and immunologic diseases the Institute strives: 1) to recognize and define a set of the important national public problems whose solution would probably be helped by increased research effort; 2) to decide upon the nature and extent of federal intervention in the research process judged most likely to expedite the finding of a solution and 3) in the long term national interest to support a large body of free ranging, problem oriented, investigator-inspired research and the appropriate research training.

The selection of mechanisms for Federal intervention and deployment of resources are Institute decisions. The mechanisms chosen are inextricably mixed with the specific program objectives and therefore with advice from expert groups on what those objectives are and how they could be reached. But specific program objectives fall into the following general types for which certain mechanisms are useful:

- for quicker translation of research findings into better patient care--categorical clinical centers
- for research and development of specific methods for better prevention, diagnosis, treatment or control of disease--directed programs largely of federally managed contracts
- for improved technical support of research--directed programs largely of contracts for resource (reagent) production and distribution
- for stimulation of research interest and increased recognition of the importance (or neglect) of problems--structured workshops and Special Emphasis Programs (SEP)
- for expedited communication to telescope research lead time and minimize overlap--a limited number of scientific memoranda dealing, on a continuing basis, with the latest unpublished information on a specific disease/disease problem
- for increased investment in the attack on problems best solved by individual research project approaches--preferential funding of grants in SEP by Dollar Allocation to Program Areas (DAPA).

Special Activities

Three programs merit special comment if only because they cut across disciplinary lines and are unique to the National Institute of Allergy and Infectious Diseases. They are the United States-Japan Cooperative Medical Science Program, the International Centers for Medical Research and the Scientific Communications Program.

The U.S.-Japan Cooperative Medical Science Program was begun in 1965 following a meeting between the Prime Minister of Japan and the President of the United States. Both governments appoint biomedical scientists to constitute a U.S.-Japan CMSP Committee who in turn advise on scope and direction of the Program and develop procedures for review of program and projects to ensure fulfillment of the Program's purposes.

This joint research effort is focused on widespread diseases of great concern to Asian nations. The original interest in cholera, leprosy, tuberculosis, the parasitic diseases--filariasis and schistosomiasis, malnutrition and certain viral diseases has recently been expanded to include research concerned with methods for evaluating the effect of environmental pollution on cancer and genetically induced birth defects. Each major disease area has its own expert panel for program review and advice on specific program goals. Projects proposed by U.S. scientists and relevant to these goals are reviewed for merit by the regular NIH study section system.

The National Institutes of Health provides funding for the support:

- of research projects proposed by U.S. scientists;
- of scientific meetings held in the United States; and
- of the U.S. Panel members and consultants to attend Program meetings.

The Japanese Ministries of Health and Welfare and of Education assume a similar responsibility for their counterpart activities.

The U.S.-Japan CMSP has been recognized as a model for effective international scientific cooperation not only on a diplomatic but also scientist to scientist level.

An annual scientific report is made to Congress by the President.

The International Centers for Medical Research (ICMR) Program was established in 1960 in accordance with the expressed desire of Congress to advance the status of health sciences in the United States and thereby the health of the American People. An ICMR is a discrete research organization, sponsored by a medical or public health school which provides a stable continuing base on which to conduct programs of biomedical research, research training and planning, both in the United States and abroad, through the development of a cooperative working agreement with an established foreign research center. This cooperative affiliation has several advantages. It provides:

- opportunities for research not available in the United States
- career stability for the U.S. investigator in the foreign setting
- a cadre of U.S. investigators with interest and expertise in the problems of geographic medicine as they may affect U.S. interests
- a U.S. presence abroad in biomedical research.

The ICMR program has its own panel to review and advise on program and policy which from time to time are presented to the Advisory Council of the National Institute of Allergy and Infectious Diseases.

The Scientific Communications Program is in addition to the classical activities related to scientific publications and meetings, and is an attempt to develop new or improved methods for scientist to scientist communications. The two current projects are feasibility studies for the development of the use of scientific memoranda, and communication satellites.

The Scientific Memoranda project is devoted to the development of a new means for fast and informal communications on current research by active investigators in a relatively small well defined field. Normally, from 9-18 months elapse between completion of an experiment and publication of the results in scientific journals. Through the Scientific Memoranda, short progress reports, summaries, negative data, technique modifications, and other informal communications are interchanged on a monthly, bimonthly or quarterly basis. This ability to communicate quickly, within the comparatively small group of participating investigators who are most active in a given research area, permits significant savings in research time and expenditures. The Memoranda do not replace the archival role of scientific journals. The six current Scientific Memoranda are concerned with research on: interferon, hepatitis, leprosy, hypersensitivity disease and transfer factor. Participants in these projects total almost 1,000 and are located in 53 countries.

The Satellite Communications project is a feasibility study to develop the use of satellite transmissions for scientific communications. Initial activities are devoted to voice and facsimile transmissions between scientists conducting field investigations in isolated areas and base laboratories, and between laboratories in widely scattered and isolated sites not serviced effectively by other means of immediate communications. A valuable mechanism for emergency medical transmissions is also resulting from these studies.

Summary

Although considerable space has been devoted to describing the different types of Institute Programs, Subprograms and Federal intervention it should be recognized that all of these are based on and developed from a great body of investigator-inspired, problem-oriented individual projects. These include research and training awards and projects concerned with numerous diseases and disease related problems relevant to the Institute's mission. The projects represent the best judgments of over 4,000 scientists as to what the most significant problems are and the techniques and approaches most apt to yield new and important knowledge or tangible results. In the aggregate they cover an astounding array of diseases, organisms, problems and expertise. In their diversity and high quality lies their short- and long-range value. Quite properly this creative activity remains unmanaged as to science and therefore untargeted and unfettered except in the most general sense of relevance to the Institute mission.

DESCRIPTION OF PROGRAMS AND SUBPROGRAMS

Allergic and Immunologic Diseases

Introduction

The most rapidly developing activity for several years in the Institute's program has been research on allergic and immunologic diseases. Research directed toward acquiring better understanding of the immune mechanism is based on such scientific disciplines as cell biology, immunochemistry, and immunogenetics. Results of this research have broad application to a variety of disease problems. These include, for example, immediate type hypersensitivities or allergies, immune deficiency diseases, and of course, the more common infectious diseases. Defects in immune functions involving neoplastic cellular proliferative processes are also receiving increased attention.

Institute Programs

Asthma and Allergic Diseases

Recently, NIAID decided that the scientific base of knowledge of allergic diseases was sufficiently advanced to give promise of fruitful application. Accordingly, the Institute has now established grant-supported Asthma and Allergic Disease Centers at 17 institutions. Strong laboratory research programs are already in existence at all of these places, and the new support permits establishment of related clinical studies of allergic individuals, primarily on an outpatient basis. Major investigations underway at the centers include: methods of classifying, diagnosing and treating various clinical forms of asthma in children; immunotherapy of asthma using polymerized ragweed antigen E; effectiveness of allergoids in desensitization; reactions to stinging insects; diagnosis and treatment of allergic skin diseases; and production of IgE antibodies.

One Center is located within the intramural program of the Institute. Using patient facilities of the NIH Clinical Center, NIAID investigators are carrying out studies which focus on the biochemical pathways of mediator release and the mechanism of tissue injury in allergic diseases. Enzymatic pathways are being evaluated in patients with various types of chronic angioedema and chronic urticaria. Identification of the vasoactive mediators liberated in such patients and further characterization of the enzymatic interactions which lead to their elaboration and destruction should result in a better understanding of the pathophysiology of these diseases and to the development of new modes of therapy.

NIAID has recently made available funds for allergy research training under NIH Institutional Research Fellowship Awards and Allergic Diseases Academic Awards. Both categories of awards will assist nonprofit institutions in establishing or strengthening allergy research programs and, simultaneously will help young medical scientists broaden their scientific background in the field of allergy.

Collaborative efforts in the area of asthma and allergic diseases are expanding. Antigens E, K, and Ra3 from short ragweed pollen have been made available to qualified investigators and a polyvalent antiserum against the antigens of ragweed pollen is being prepared. When packaged for distribution, this antiserum will provide a long-term reference material for serologic assay of the predominant antigens in ragweed pollen. Group antigens of rye grass pollen are being extracted. Plans are being made to produce an antiserum against human IgE. This reference reagent will be particularly useful to laboratories conducting the radioallergosorbent (RAST) test as a means of diagnosing allergic diseases.

Clinical Immunology

Closely related to the Asthma and Allergic Diseases Program is the research area of clinical immunology. The Institute is sponsoring coordinated efforts in clinical immunology in a few key grantee institutions so that this scientific discipline can be applied to a broader spectrum of patient problems.

Among the essential elements of this Special Emphasis Program are (1) identification of the incitants of immediate type hypersensitivities; (2) full characterization of primary immune deficiency diseases; (3) more complete evaluation of secondary immune deficiencies; (4) development of methods for the assessment and reconstitution of failure of immune competence; (5) recognition of the factors involved in the loss of natural tolerance expressed as autoimmune diseases; (6) recognition of the nature of immune defects occurring secondary to the development of malignancies; and (7) establishment of the enzymatic and biochemical basis for immunologically mediated tissue injuries, such as immune complex disease.

Investigator-inspired research on clinical immunology within the intramural program of NIAID includes studies of tumor immunology. NIAID investigators, in some instances working closely with National Cancer Institute scientists, are carrying out pioneering work in identification of the origin of malignant human reticular cells. The procedures being developed by these intramural scientists should become useful diagnostic tools which will permit clinicians to distinguish among the many kinds of tumors of the human lymphoid system and, on this basis, to make rational therapeutic choices.

Throughout numerous NIAID laboratories are other studies related to immunology and disease. For example, one group of scientists is studying differences in graft-versus-host disease in hybrid mice of the same genotype and have found that factors other than genotype can determine the outcome of such reactions--a finding that may ultimately have therapeutic importance. Other scientists are using "nude mice" in attempts to establish an animal model of the human disease, lupus erythematosus; while still others are engaged in basic studies aimed at delineating the precise mechanisms whereby immunosuppressive agents affect the immune response in man and experimental animals.

NIAID collaborative efforts in immunology and disease have focused, largely, on the development and coordination of methods, procedures, and resources which will enhance research in transplantation immunology. For almost 10 years, Institute staff has worked with contract-supported investigators to obtain and make available high-quality histocompatibility reagents for tissue matching research. A crucial and increasingly important effort is the collection and dissemination of information on organ transplants and the relationship of graft survival to tissue matching, particularly in regard to organs from cadaver donors.

Through its collaborative program, the Institute participates in the support of a network of tissue typing centers and provides reagents necessary for this work. The quality and value of these typing reagents is insured by quality serum control laboratories and regional typing evaluation facilities.

A fluorescent, labelled antihuman IgM serum is being procured in a cooperative effort with the International Union of Immunological Societies and is intended to serve as a World Health Organization International Standard.

Recently, emphasis has been placed on immunosuppressive agents for use in transplant recipients and particularly on antilymphocyte serum. Future plans call for an expansion of efforts which will place emphasis on studies of immunologic enhancement and tolerance, the development of reagents for basic research in immunology, particularly those needed for studies of allergies and other immunologic diseases, and consideration of the clinical use of the cell product known as transfer factor.

Institute Subprograms

Lymphocyte Biology

Basic to the development of better means of preventing and controlling disease is a better understanding of the variability and activation of immunocompetent cells, particularly the lymphocytes. A Special Emphasis Program established by NIAID has as its ultimate goal attainment of more complete knowledge of the life history of these cells and of the genetic factors that determine their fate in vivo and in vitro. Such information might make it possible to utilize selected cloned lymphocyte cells and their products to support or reconstitute immunologically deficient recipients to alleviate allergic states, to provide resistance to life-threatening infections, and to cope with neoplasia.

In the advancement of this program, the techniques and ideas of cell culture, cell biology and many other disciplines have been integrated into multi-disciplinary program projects. Such broadly-based, NIAID-supported projects are presently underway at several institutions.

In addition, intramural scientists, armed with sophisticated tools of immunogenetics and immunochemistry, are studying the ontogeny and heterogeneity of lymphocytes, the nature and function of antigen-binding membrane receptors of lymphocytes, and the mechanisms of tolerance induction and lymphocyte interactions. Major efforts are being exerted by these scientists to elucidate the nature, genetics, and mode of function of specific immune response gene products, the mechanisms of cell-mediated cytotoxicity, the nature of genetic and chemical control of immunoglobulin synthesis and variability, and the activation of immunocompetent cells.

Cell-mediated Versus Humoral Antibody Response

It is now evident that the humoral and cellular immune responses are not totally independent. They interact with each other in ways that can either inhibit or potentiate one another. There appears to be an inverse correlation between these two major expressions of the immune response: high levels of a cell-mediated immune response tend to be associated with low levels of humoral antibody formation, and vice-versa. To control the nature of this dual immune response, T and B cell interactions must be examined in more detail and must be better understood.

Aware of the potential for disease control inherent in this area of research, the Institute has established a special emphasis grants program which encourages investigators to seek the knowledge which will provide the capability to selectively manipulate the immune response. Such capability would be an asset not only in the prophylaxis and therapy of infectious disease, but would also find application in tumor immunotherapy, transplant acceptance, and control of aging syndromes.

Intramural studies in this area are significant. For example, one group of NIAID scientists has been working with lymphocytes activated to DNA synthesis by plant mitogens. One particularly important stimulant is pokeweed mitogen which has been reported to activate both T and B lymphocytes. Although five distinct stimulatory substances have been extracted from pokeweed, only one seems capable of stimulating both T and B lymphocytes. Studies are now in progress to delineate the chemical characteristics of this substance and to use this knowledge to determine the relative molecular requirements for T and B lymphocyte activation.

Other NIAID scientists have recently found that two classes of functionally active thymus-derived (T) cells can be separated from each other. Results of this research give further support to the concept that the pool of thymus-derived lymphocytes is composed of subpopulations of cells, each with discrete and limited functional capabilities.

NIAID clinical studies of chronic candidiasis as a model of defective cell-mediated immunity have been and continue to be fruitful. Various classes of patients have been characterized clinically and immunologically and their treatment thus facilitated. One mode of therapy--restoration of cell-mediated immunity with transfer factor--has been found beneficial and studies are now in progress to determine the mechanism of action of this substance and characterization of its physical and chemical properties.

Infectious Diseases

Introduction

Bacterial, fungal, parasitic, and viral infections are a frequent and increasing hazard, especially for the very young, the aged, the hospitalized, and for those--such as cancer patients--who receive immunosuppressive therapy.

While many infectious diseases have been controlled by vaccines or antibiotic therapy, substantial problems still exist. Virtually no effective antiviral therapy is yet available for general use and many enterprising bacteria seem to be not only changing their infectivity through genetic modification but also to be increasing their resistance to antibiotics.

The Institute is concerned with seemingly mild viral diseases, such as upper respiratory infections, because of their enormous aggregate socioeconomic impact. NIAID is also concerned with lethal viral diseases, such as influenza, and with the subtle long-term role probably played by viruses in chronic and degenerative diseases. Better control of viral diseases depends, in turn, on obtaining a better understanding of the complicated ways in which the body responds to virus infection, with the intricate way in which viruses attack and invade body cells, and with the demonic way in which viral genetic material apparently can create biological monsters, such as tumors.

Research on the fundamental aspects of bacterial and fungal disease has as its goal the development of clinical techniques required to eliminate or lessen the impact of these diseases on the Nation's health. The program is wide ranging, based on such biomedical sciences as microbiology, immunology, and biochemistry, and focused on such bacterial diseases as tuberculosis, staphylococcal and streptococcal infections, meningitis, and pneumonia. Bacterial and fungal infections found in the hospital environment or in patients with impaired immune defenses are of particular concern.

Parasitic infestations are still common in the United States. They also impose an enormous burden on the health of millions living in the less developed nations of the world. Jet travel and the consequent shrinking of elapsed time between a foreign country visited and the visitor's return home have reintroduced U. S. physicians to such diseases as malaria, once thought eradicated from this country.

Institute Programs

Venereal Disease

Several years ago NIAID held a workshop of experts to explore the problems relating to the current alarming increase in gonorrhea in the United States. The experts considered many aspects of this major health problem, and recommended a number of research objectives to further our understanding and to aid in control of this disease. These research objectives were developed into a new Special Emphasis Program on the biology of the organism causing gonorrhea. A similar workshop held a few months later on the problem of syphilis resulted in the addition of Treponema pallidum infections to the program now known as "Biology of Venereal Diseases."

The goal of this program is to encourage investigators to undertake research which will provide much needed information relating to the basic biology and immunology of sexually-transmitted diseases. This knowledge may be obtained through studies of the growth, nutrition, and physiology of the organisms causing venereal disease. Purification, characterization, and determination of the structure of cellular antigens of the organisms will be pursued. Specific antibody development, cellular and humoral defenses, and mechanisms of recurrent infection or reinfection are also under study. A major research effort is being devoted to development of experimental animal model systems for the human infections and of tissue culture methods for study of the microorganisms. In light of the growing resistance of some of these organisms to currently available antibiotics, investigators are being encouraged to explore the underlying mechanism of antimicrobial action and to undertake therapeutic and clinical studies with a variety of antimicrobial agents.

In order to expand biomedical research in the field, a program of NIH Institutional Research Fellowship Awards has been set up. These awards will assist nonprofit institutions in providing young health scientists and clinicians opportunities for postdoctoral study in venereal diseases.

A small collaborative program in venereal disease has been initiated with the award of several contracts for the in vitro cultivation of Treponema pallidum. Cultivation of this organism in a tissue culture system is considered of paramount importance for research on syphilis and for the possible development of candidate immunizing agents. An ad hoc meeting of experts in the field of venereal disease, brought together by NIAID in 1973 recommended a number of other projects appropriate for contract funding and these are being considered in the program planning.

Hepatitis

Viral hepatitis, a disease of major public health importance, has long been the target of intensive research by many capable investigators. A Special Emphasis Program on hepatitis, within the grants area, has encouraged and supported efforts to isolate the etiological agents and to determine the best methods of growing these for vaccine development and production.

In addition, a vigorous collaborative program, spearheaded by intramural scientists, was initiated only a few years ago and is already beginning to pay off. For example, a team of intramural scientists, using immune electron microscopy, recently "visualized" an agent believed to cause hapatitis A (infectious hepatitis) while another group of intramural and contract-supported investigators produced convincing evidence that the so-called Dane particle, one form of the hepatitis B antigen (Australia antigen), is probably a virus and the cause of hepatitis B (serum hepatitis).

A number of projects following up these findings are underway or planned. In order to help identify "high risk" populations for future passive or active immunization trials, the Institute is planning collaboration with the National Heart and Lung Institute to determine to what degree hemodialysis patients and close contacts of these patients can be classified as "high risk" for hepatitis B. Another epidemiologic study is being conducted at a state school for the retarded. Screening for both hepatitis B antigen and antibody in residents and staff members has begun with continuing close surveillance of new admissions to the school.

Progress is continuing in collaborative efforts to characterize the agent of hepatitis B in animal models. Primates closest to man, notably the chimpanzee and the rhesus monkey, appear to be the most susceptible to hepatitis B infection. In fact, response to the hepatitis B antigen seems to be identical in chimpanzees and man. Pedigreed pools of infectious hepatitis B material have been derived from chimpanzees and will serve as challenge pools for future active immunization tests in animals.

Because the marmoset has been shown to be susceptible to hepatitis A infection, NIAID, in cooperation with the Center for Disease Control (CDC) and FDA's Bureau of Biologics, has established and is maintaining a marmoset colony. Such a colony will ensure the availability of small animals for stepped-up hepatitis A research. However, recent experiments have suggested that the chimpanzee, also, can be infected with hepatitis A virus and will thus, serve as an animal model for the disease.

Currently some of the most sensitive techniques for the detection of hapatitis B virus antigens in tissue are immunohistochemical assay procedures. Scientists, working under contract, are applying these techniques to the detection of hepatitis B antigens, particularly in specimens from animals involved in hepatitis infection experiments. Results of these studies have had a major impact on scientific understanding of the various forms of the hepatitis B antigen.

A hepatitis testing laboratory at the American Red Cross is supported by Institute contracts. In this facility investigators can have research material tested for hepatitis antigens and antibodies by the most sensitive techniques available. An additional function of the laboratory is to aid in the standardization of methods for detecting hepatitis antigens and antibodies.

Another NIAID-supported laboratory engaged in hepatitis research is the Rockville Laboratory of the Molecular Anatomy Program (MAN), a cooperative project of NIAID and the U.S. Atomic Energy Commission. This laboratory has as its major objectives the development of methods for isolating and purifying viruses and viral antigens and the application of these techniques to research on associated diseases. The training of NIAID intramural scientists and contractors in the research application of the specialized instrumentation developed by the MAN program, particularly the zonal centrifuge, is also an important aspect of the laboratory's mission.

Current hepatitis research at the Rockville laboratory is focused on chemical characterization of the recognized subtypes of hepatitis B antigen and preparation of subtype-specific reagents for use by investigators. Recently emphasis has been placed on use of the hepatitis B antigen specific DNA polymerase as a marker of hepatitis B virus infectivity.

Influenza and Other Respiratory Infections

Influenza is a major respiratory disease in terms of morbidity and medical care costs. Fortunately, the influenza virus is readily studied in the laboratory and scientists working on this organism have learned to manipulate it genetically and to study it in depth biochemically.

Grantees--supported in a Special Emphasis Program--and intramural scientists have made major contributions recently to influenza research. Their findings are being applied to Institute efforts to develop vaccines tailor-made to cope with "new" influenza A viruses as they appear on the world scene.

The appearance of these pandemic influenza viruses at approximately 10 year intervals has sparked considerable research on their origin. According to NIAID grantees and others, these "new" viruses are probably recombinants formed as the result of mixed infection of a barnyard creature (such as a horse, a duck, or a pig) with human and nonhuman strains.

Research which has brought this situation to light is based on the grant-supported development of sera specific for each of two chemical substances--hemaglutinin and neuraminidase--found on the surface of the influenza virus. Using these sera, scientists have found evidence that the hemaglutinin of the human Hong Kong virus is closely related to hemaglutinin subunits of two strains of influenza virus isolated from horses and ducks 5 years before the Hong Kong strain appeared. Analysis of the chemical structure of the hemaglutinin of the three strains (Hong Kong, duck, and horse) revealed even more similarities and NIAID grantees now speculate that the three viruses arose, by genetic recombination, from a common ancestor.

The immediate practical application of results of this grant-supported research has been the development of techniques for identifying surface antigens of the influenza virus. In fact, a new type of influenza vaccine is now under development against the neuraminidase antigen alone. Of even more future importance is use of these antigens for possible identification of influenza viruses in animal hosts that may serve as the source of pandemic viruses for man.

Intramural scientists have been engaged in a different approach to the genetic manipulation of the influenza virus as a means for the development of more effective vaccines. They have found that temperature sensitive (ts) mutants of the influenza virus can be grown in the laboratory. Using one of these ts mutants as a prototype live vaccine, the scientists found that it replicated only in the cooler passages of the upper respiratory tract and not in the warm area of the lungs where influenza does its greatest damage. Furthermore, the live ts mutant vaccine provided protection in volunteers challenged with the wild-type influenza A virus.

NIAID investigators are now trying to elucidate the nature of the genetic lesions present in the ts mutants produced in their laboratory. The scientists intend to produce single mutants with lesions specific for each of the genes of the influenza A virus. Such a set of stable, single lesion mutants are expected to prove invaluable as genetic probes for characterization of the lesion or lesions transferred from an older ts vaccine strain to a recently emerged, epidemic strain possessing new surface antigens. Availability of single lesion ts mutants will also allow scientists to define the relationship between sites of genetic change in the genome and attenuation for experimental animals and man.

Attempts are being made by intramural scientists to produce conditional, lethal temperature sensitive mutants of other respiratory disease agents. These include respiratory syncytial virus and parainfluenza virus--serious pathogens of infants and young children--and Mycoplasma pneumoniae which is a major cause of disease in young adults. Tests of clinical acceptability, antibody response and efficacy of these ts mutant vaccines as well as inactivated vaccines are either underway or planned.

New techniques for the recovery of viruses from patients with respiratory disease are being explored by intramural and grantee scientists. For example, specimens obtained from individuals enrolled in common cold studies are first examined by routine cell culture methods and those which fail to yield viruses are studied further in experimental culture systems which include human embryonic trachael organ cultures. Use of the new systems has been especially fruitful in the recovery of virus strains belonging to the human coronavirus group. Since the coronaviruses appear to be important etiologic agents of adult upper respiratory tract illness, continued intensive efforts are being made to develop new ways to detect and propagate these agents.

Contract-supported scientists were enlisted in a formal collaborative program on influenza in FY 1974. The long-range goal of this program is to support research activities leading to knowledge that will abort or lessen the impact of future epidemics and pandemics. Areas of research support are being closely coordinated with other agencies of the Government (particularly FDA, CDC, and the Army) in order to avoid unnecessary overlap or duplication of efforts.

A major effort of the collaborative program has been devoted to evaluation of attenuated influenza A virus vaccines developed by intramural scientists. One ts mutant vaccine has been tested in various pediatric populations and appears safe and immunogenic, with no illnesses resulting from vaccination. Vaccines of various clones of ts mutant recombinants have also been prepared under contract and tested in normal adults. These studies are not only helping to determine the protective effect of the vaccines; they are also providing basic information on the genetic and biochemical background of the ts lesions.

An experimental inactivated influenza vaccine monospecific for the neuraminidase surface antigen is being evaluated in Texas, where NIAID has established an influenza research center. The center will serve as a national focus of research efforts to find answers to many of the puzzling questions surrounding influenza. A team of experienced investigators there will set up studies designed to clarify pathogenic, epidemiologic and immunologic aspects of influenza, evaluate licensed and experimental vaccines, and explore the potential of antiviral substances in preventing or treating the disease.

Development of New Vaccines

Vaccines for respiratory pathogens other than the influenza virus are being developed and evaluated through collaborative efforts. Monovalent and polyvalent vaccines of pneumococcal capsular polysaccharides have been prepared and clinical evaluation studies are in progress. Studies of the clinical acceptability, antibody response, and efficacy of these pneumococcal polysaccharide and of an inactivated *M. pneumoniae* vaccine are underway.

Collaborative efforts are also focused on the development of vaccines against two organisms--*H. influenzae* and *N. meningitidis*--primarily responsible for bacterial menigitis in young children and infants. A candidate *H. influenzae* type b polyribose phosphate vaccine has been developed by NIAID contractors and is being clinically evaluated in children.

Clinical studies in children of groups A and C meningococcal polysaccharide vaccines are also being carried out by NIAID contractors. A large-scale trial to determine the efficacy of group A meningococcal polysaccharide vaccine and the *H. influenzae* type b polysaccharide vaccine is presently underway in Finland where outbreaks of meningitis caused by the two organisms have occurred frequently.

An octovalent pneumococcal polysaccharide vaccine--originally developed for use in the elderly--is being studied in infants and children. Plans are being made to evaluate the effectiveness of this preparation in preventing acute otitis media--a very important childhood disease affecting all races and social classes.

Both grants and contracts are used to support research on the development of a more effective cholera toxoid or vaccine. This is a part of the U.S.-Japan Cooperative Medical Science Program and includes continuing studies on oral immunization.

The advent of an oral cholera vaccine may offer a new approach to cholera immunization. It is believed that the fluid loss caused by cholera toxin is due to the attachment of the toxin to the cells of the intestine. Animal studies have indicated that locally produced antibodies in the intestine may interfere with this attachment.

In a spin-off from the cholera program, investigators are studying similarities between enterotoxins produced by _E. coli_ and _V. cholerae_. The immunological relationship between these two organisms has been firmly established by cross-neutralization tests. Because of these and other recent rapid advances in knowledge of _E. coli_ enterotoxins, the NIAID is planning a study to determine the magnitude of the disease problems caused by _E. coli_ toxins and the need for control measures, such as an effective vaccine.

Also within the U.S.-Japan program are studies of the immunological aspects of tuberculosis. Through several contracts, highly characterized and standardized mycobacterial materials are made available to qualified scientists. A monkey model for studying aerosol BCG vaccination with aerosol challenge has been investigated. Since there has been some concern that repeated vaccination via the aerosol route might elicit a type of hypersentitivity reaction in the host, guinea pigs have been sensitized and vaccinated with aerosolized BCG organisms and no adverse effects observed.

Antiviral Substances

Research on antiviral substances is an active component of all three segments of the Institute program--extramural, intramural, and collaborative studies. The extramural program supports scientists conducting basic research on how drugs and other antiviral substances work in the cell and in animals. Grantees--as part of a Special Emphasis Program--are engaged, particularly, in investigations of the structure of interferon since this information is needed for meaningful attempts at synthesis.

Intramural scientists have been involved, for some time, in studies of interferon and interferon inducers and their effect on immunity. They have recently developed a new type of interferon inducer which is stable, relatively non-toxic, and potentially useful in treating a variety of infectious and malignant diseases.

The collaborative program supports contract research on development and purification of exogenous interferon and development of rapid assays for interferon and other antivirals. Contracted research also includes measurement of the protective effect of these antivirals in various animal-model systems and in humans with a variety of viral diseases. When the collaborative program was launched, interferon and interferon inducers seemed to be the most promising antivirals for exploitation. This continues to be the case, although one drug--adenine arabinoside (Ara-A)--has, more recently, shown effectiveness, against herpes encephalitis and other serious viral diseases. This compound is now being carefully evaluated.

An NIAID Interferon Scientific Memoranda, containing progress reports, research notes, and negative data and comments, goes out to scientists in the field who participate in this exchange of research information. In addition, an annual Interferon Bibliography is published.

Hospital-Associated Infections

Hospital-associated infections are a problem of the utmost gravity, not only in the United States, but in other advanced countries, as well. These infections contribute directly to the spiraling cost of medical care and are responsible for a large number of deaths.

A Special Emphasis Grants Program in this area is designed to enlarge fundamental knowledge of the multiple factors involved in the causation of hospital-associated infections. The long-range goal of the program is, of course, the application of new knowledge to develop methods for the prevention and treatment of nosocomial infections.

The Special Emphasis Program includes host resistance studies. The full range of the normal resistance process against the microbial flora commonly encountered in every day situations will be explored since many of the organisms threatening hospitalized patients do not commonly pose a health threat to normal individuals. Examination will be made of the effects of debility, metabolic disturbances, and cytotoxic therapy on the capacity of humoral components and the cellular immune system to counter the effects of various microorganisms.

One grantee has been studying the clinical pharmacology of antibiotics, particularly in the debilitated patient. He has found that oral antibiotic excretion or retention patterns vary widely among patients. This is particularly important for the severely debilitated or those with burns. Such patients, including those with renal failure, absorb large amounts of neomycin, leading to neomycin toxicity. Regulation of therapy in such patients requires, therefore, frequent and careful measurements of drug levels.

Of particular concern to clinicians caring for hospitalized patients are the systemic mycoses. Although most fungal diseases, such as cryptococcosis and candidiasis, can be treated with amphotericin B or similar chemical compounds, these drugs are highly toxic and cannot always be given in fully effective doses.

Grantees at one institution have developed, over the years, a promising new method for treating serious fungal infections, using a combination of drugs. Working with tissue cultures of pathogenic fungi, the scientists found that amphotericin B could be used to increase the antifungal effects of several antibiotics.

In studying the reason for this synergistic effect, the grantees found that amphotericin B "makes holes" in fungi cell membranes. Other drugs, such as rifampin, penetrate through these holes and interfere with RNA synthesis. Knowledge of the mechanism behind this synergism should enable scientists to work out, on a rational basis, improved methods of treating systemic fungal infections.

The chemotherapy and immunology of systemic mycoses is a major concern, also, of NIAID clinical investigators. They have been engaged in examining the humoral and cell-mediated host response during cryptococcosis infection in man and experimental animals. The investigators have found that human peripheral blood mononuclear cells can kill the encapsulated fungus by an antibody-dependent, non-phagocytic mechanism. Importance of the alternate complement pathway in phagocytosis of cryptococci has also been underscored by these investigators' discovery that antibody-coated cryptococci are poor receptors for early components of the classical pathway.

Pseudemonas pneumonia is another hospital-associated infection receiving attention from investigators. Over the years clinicians have found that the bacteria causing this infection are relatively resistant to a number of antibiotics and often cause fatal disease in patients with malignancies, aplastic anemia, or severe burns. Transplant patients who receive immuno-suppressive drugs are also at increased risk of pseudomonas pneumonia.

In order to determine if transfusion of granulocytes would help restore the ability of these patients to fight pseudomonas or other bacterial infection, intramural scientists recently developed an animal model system in which to study the effectiveness of this procedure. Dogs were given a high dose of radiation to eliminate the majority of their white cells and then were infected with Pseudomonas aeruginosa. Later, the animals were given either an antibiotic--gentamicin--alone or in combination with transfusions of granulocytes from normal dogs of a different breed.

Results of this randomized controlled trial in an experimental animal indicated that granulocytes significantly prolonged survival, promoted clearance of the organisms from the lungs, and prevented shock. This demonstration of the effectiveness of granulocytes in an animal model should prompt further clinical studies to define the specific circumstances in which granulocyte transfusions are of most benefit to man.

Future Institute plans call for establishment of a collaborative program in the area of hospital-associated infections. At present a series of workshops are being held to identify the disease agents causing the most trouble and to determine research approaches which might be taken by contract-supported scientists.

Institute Subprograms

Mechanisms of Resistance to Antimicrobial Agents

During the past 10 years, the importance to health problems of microbial resistance to therapeutic agents has become increasingly apparent.

The relevance of this phenomenon to other NIAID interests is obvious. Most of the projects in the Special Emphasis Program in this area are directed toward elucidation of the fundamental biological mechanisms involved in the development of drug resistance. Specific research goals include investigation of genetic characteristics, such as the R factor, and epidemiological interrelationships of this and other drug resistance plasmids. A special effort is being made to learn how to control genetic expression of drug resistance. Mechanisms of antibiotic inactivation and the molecular basis of plasmid and bacteriophase control of toxin production are also under study.

Drug-resistant strains of malaria, particularly those resistant to chloroquine, have been of research interest to intramural scientists for a number of years. Strains of P. falciparum that are resistant to all of the commonly used synthetic antimalarials, as well as to quinine, continue to be encountered in widely separated areas of the world and other species of malaria infecting man may also become refractory to presently effective drugs. Intramural scientists have found Plasmodium berghei, a strain of malaria infecting rodents, a valuable laboratory model for the investigation of the mode of action of various antimalarial compounds and for elucidation of some of the basic aspects of acquired drug resistance in malarial parasites.

After years of treatment, leprosy bacilli sometimes become resistant to DDS--the drug of choice for treating this ancient disease. In fact, it has been estimated that as many as one percent of newly treated patients may eventually develop infection that is resistant to DDS.

In the search for new and better antileprosy compounds, scientists have obtained support from grants and contracts administered by the U.S.-Japan Program. Data are being gathered regarding the effects of a three-year mass chemoprophylactic treatment of leprosy with DADDS--a derivative of the older drug. Preliminary evidence from this study suggests that the effectiveness of prophylactic DADDS continues after administration of the drug is stopped and that this effect is truly preventive, and not merely suppressive.

The NIAID sponsors a Scientific Memoranda on leprosy in an effort to speed communication between investigators in this field. Scientists participating in this Memoranda are located both in the United States and foreign countries.

Streptococcal Disease and Sequelae

NIAID has had for some years a Special Emphasis Program on streptococcal diseases and sequelae, since widespread use of antibiotics has not eliminated these most common bacterial infections. There are still many gaps in scientific knowledge relating to diseases of streptococcal origin, particularly the serious sequelae resulting in rheumatic heart disease and in renal complications.

The grants program is currently focusing on two areas: the biology of the streptococcus; and the pathogenesis and clinical aspects of streptococcal disease. Studies are being carried out on the antigenic mosaic of streptococcal cell walls with special attention being paid to surface polysaccharides and M protein. Exotoxins, pyrogens, and enzymes are also under investigation.

Intramural scientists continue to make important contributions to knowledge of the streptococcal organism. They have developed new procedures for isolating and characterizing the M protein and are studying "difficult" but common serotypes of streptococci whose type-specific and protection-inducing M proteins would need to be included in any useful polyvalent vaccine.

Collaborative research, supported by NIAID, has already led to the development of a candidate M protein which is currently being evaluated in adult volunteers for safety and immunogenicity. The vaccine is being given intranasally and seems to prevent subsequent colonization with challenge organisms. It is hoped that this observation will be confirmed in further trials and that the vaccine may be particularly useful, therefore, in reducing the number of potential carriers and, thus, greatly diminishing the community reservoir of infection.

Chronic and Degenerative Diseases of Man

The causes of a number of chronic and degenerative diseases of man are not known but findings obtained from studies of a few of these human illnesses and of several in animals suggest that viruses or virus-like agents may play a central role.

A Special Emphasis Program is supporting work by investigators who are trying to isolate viruses and virus-like agents from chronic and degenerative diseases of unknown etiology. These include multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and chronic renal diseases. Virus and virus-like agents that appear to have an etiologic relationship to chronic and degenerative diseases of animals are also under investigation.

Intramural scientists have been actively engaged in the study of some of the latter infections which may serve as animal models for the human diseases. They have been particularly interested in scrapie (a subacute polio-encephalopathy of sheep) and in a comparable disease of ranch mink. Aleutian disease of ranch mink and progressive pneumonia in sheep are also under study. Investigations of these chronic viral diseases of animals provide a point of departure for a fresh attack on disease problems heretofore considered outside the realm of infections.

DNA viruses of the papova group--long recognized as having oncogenic potential for man--are now under investigation by intramural and other scientists who believe they may be importantly associated with unexplained degenerative human diseases. Evidence has been obtained that under certain circumstances they may infect individuals and persist independently, causing a slow, demyelinating disease.

Clinical Virology

Within the past year, a Special Emphasis Program on clinical virology has been established in response to an apparent need for a better understanding of the pathogenesis of human viral infections. This clinically oriented knowledge is lagging behind contemporary discoveries in molecular virology. The Special Emphasis Program aims to merge the talents of young investigators well versed in the technologies and concepts of modern virology with those of clinical investigators, ideally in the setting of a hospital-based virus diagnostic laboratory.

Among investigations supported by grants are development of rapid, sensitive, and economical laboratory methods of diagnosing the more common viral infections. Investigations on effects of the route of administration of viral immunogens will also be supported since this could affect the distribution and character of the resultant human host immunity.

An example of intramural research which has made a significant contribution to this area, is the NIAID investigations of acute non-bacterial and non-parasitic gastroenterisis. These studies have been particularly productive during the past few years. First, an agent causing outbreaks of gastrointestinal disease in a number of widely separated communities was identified. Called the "Norwalk agent," this small virus was first observed and specifically identified by intramural scientists using the technique of immune electron microscopy.

This same technique was employed most recently by intramural and other scientists in uncovering an agent responsible for infant diarrhea in this country and in Australia, Canada, and England. Scientists carrying out this research also developed a complement fixation test for the agent which should prove valuable in unraveling the natural history of this disease which causes untold deaths and suffering in infants and young children around the world. Currently, attempts are being made to grow both the Norwalk agent and the new virus in tissue culture, to determine the roles they play in non-bacterial and non-parasitic diarrhea, and, if feasible, to develop effective vaccines.

Biological Regulation of Vectors

For the past 30 years, control of disease vectors has been based primarily on the use of synthetic organic compounds which had the "advantages" of long residual action and toxicity to a broad spectrum of target organisms. Now these very characteristics are considered, in some cases, more deleterious than beneficial when all effects on man and his environment are considered. Furthermore, developing resistance to broad spectrum chemical pesticides has reduced their effectiveness in many vector control programs.

For these reasons, the search for alternative methods of pest control has become imperative. Experts believe that the best approaches will combine biological control with judicious use of more specific chemicals. This approach must be based on adequate information about the ecology of the target organism, the environment in which the control program is to be conducted, effects of control measures on non-target organisms, and the biology of the disease organisms being transmitted. A Special Emphasis Program established by NIAID in its extramural area is dedicated to achieving these goals.

Grant-supported projects in this program involve use of diseases, parasites, or predators which attack the vector. Other studies focus on the displacement of the vector from its place in the environment by an organism which does not transmit disease. In some cases, it may be possible to modify the behavior of a vector so it can be more easily killed or otherwise prevented from transmitting disease. Projects concerned with the biology or population dynamics of vectors are expected to provide knowledge on which biological control programs can be based.

Intramural scientists have been concerned, in particular, with the development of biological means of controlling the vectors of schistosomiasis and malaria. Stocks of snails with varying susceptibility to S. mansoni, the organism causing schistosomiasis, having been established and are being used for biochemical, biological, and cytogenetic analyses of the basic mechanism of susceptibility. Lines of mosquitoes susceptible or refractory to a particular species of primate malaria have also been established by intramural scientists and are held in a recently built insectary on the NIH campus. Malaria is an entomological problem, but the genetic basis for vectorial capacity is poorly understood. Development of genetically defined lines of mosquito vectors will provide important tools for a variety of research projects.

Vector-pathogen relationships are being studied by other intramural investigators interested primarily in arthropod-borne viruses and the rickettsiae which are transmitted by ticks. Attempts are being made to develop vector or vector-related tissue cultures and to apply these systems to the study of arthropod and tick-borne disease.

A significant discovery in the field of arbovirology was reported recently by NIAID grantees who found that the insect-borne LaCross encephalitis virus is passed from one generation of mosquito to the next in the female's egg. Efforts to control the spread of this vector-borne disease must take into account this new knowledge which probably explains the ability of the virus to survive freezing winters in Wisconsin where it is most prevalent.

Under the auspices of the U.S.-Japan Program, a number of contracts have been awarded for studies of vector-borne parasitic diseases. These include production of animals and vectors infected with schistosomiasis or filariasis and development of primary cell lines derived from tissues of fresh water snails.

In addition, the Institute's collaborative program has almost completed the production of seed virus and monospecific antibody preparations for over 80 arboviruses of demonstrated or potential importance to disease on the North American continent. These are available for distribution to qualified investigators engaged in research.

Immunity to Animal Parasites

The complex structure and function of parasites (particularly helminths with their marked changes during different states of development and their extensive migratory activity) have made the study of immunity to animal parasites quite difficult. However, recent developments in immunology have opened up exciting opportunities for investigations in this field. The major ultimate goal of NIAID's Special Emphasis Program or immunity to animal parasites is the development of effective vaccines for the prevention of such parasitic diseases as malaria, schistosomiasis, and filariasis. It is also hoped that better immunodiagnostic procedures for these parasitic infections can be developed.

Intramural scientists have been studying parasite biochemistry and mechanisms of energy metabolism. Their investigations are expected to provide a basis for understanding bioenergetic problems associated with parasitism, and to contribute to a more rational understanding of the host-parasite relationship which will provide information for chemotherapeutic exploitation.

Certain parasitic and tropical disease--amebiasis, schistosomiasis, trypanosomiasis, toxoplasmosis, malaria, filariasis, and dengue--are of special interest both to grantees and intramural scientists. Results of one grant-supported project may be of importance in control of two of these diseases--schistosomiasis and malaria. Investigators have found that a preparation--endod--developed for the control of disease-bearing snails may have even greater value in the control of disease-bearing insects. It was also found that the concentration of endod required to kill mosquitoes was less than that which kills snails and fish. In countries where the local manufacture of endod (an extract of the soapberry plant) is commercially feasible, its use as an insecticide should probably be further evaluated. It is hoped that field trials currently underway in Ethiopia on the use of endod in the control of snail vectors of schistosomiasis may result in concurrent control of medically important insects.

General Knowledge Development

The NIAID supports and conducts a substantial amount of research not contained in the Institute Programs and Special Emphasis Programs discussed above. This work is spread over more than 20 main categories and almost 200 subcategories of study. Many of these projects are directed toward the discovery of new knowledge which may ultimately have clinical application but which, at present, is so fundamental that it cannot be assigned to any disease category.

Such are the very important studies of how viruses infect cells, replicate, and produce the infectious or transformed state. For example, intramural scientists have been carrying out sophisticated biochemical studies of the viruses causing murine leukemia. These investigators have shown that the complete genome of a murine leukemia virus is present in the DNA of mouse cells and that virus-inducibility is dependent on inheritance of these DNA sequences. These findings--in addition to their obvious implications for virology and carcinogenesis--provide a means, for the first time, of studying a cell gene simultaneously as a functional and biochemical entity.

NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM AND DIGESTIVE DISEASES

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NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES

History

The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) was established as the National Institute of Arthritis and Metabolic Diseases by the 81st Congress through Public Law 692, enacted August 15, 1950. NIAMDD has evolved from laboratories noted for their pioneering work in experimental medicine and biology to become a center for new knowledge of genetics and metabolism, as well as of many chronic diseases characterized by their long-term disabling effects rather than mortality: various arthritic and rheumatic diseases; bone, connective tissue, skin and blood disorders; diabetes, cystic fibrosis, and other disorders of metabolism and the endocrine glands; digestive diseases and nutritional disorders; and urological and kidney diseases.

Organization

Many activities of NIAMDD are devoted to the support of research in fundamental sciences that are the foundation of knowledge pertinent to the institute disease categories: chemistry, biochemistry, enzymology, molecular biology, anatomy, histology, pathology, physiology, medicinal chemistry, pharmacology, toxicology and genetics. Simultaneously, categorical disease responsibilities cover 10 substantive areas.

Initial effort to give added direction and focus to specific needs has been in the digestive diseases and nutrition area. Current plans are to group the other categorical disease responsibilities of the institute into four clusters. Thus there will be four major subdivisions of institute activities: (1) digestive diseases and nutrition; (2) kidney, urologic and blood diseases; (3) diabetes, other metabolic diseases, and endocrinology; and (4) arthritis, bone and skin diseases. Each of the major subdivisions will be headed by an associate director with responsibility to produce a balanced program from fundamental research through demonstration and the study of improved therapies by clinical trials, using both grant and contract support mechanisms.

Intramural research will remain as presently organized under the Director of Intramural Research. The laboratories operating in relatively fundamental sciences will remain organized on a disciplinary basis, and the clinical branches, oriented toward categorical disease problems. The names of the Laboratories are as follows: Nutrition and Endocrinology, Biochemistry and Metabolism, Chemistry, Experimental Pathology, Chemical Biology, Biochemical Pharmacology, Physical Biology, Biophysical Chemistry, Chemical Physics, Molecular Biology, and Mathematical

Research. Additional branches for clinical investigations include Arthritis and Rheumatism, Diabetes, Metabolic Diseases, Digestive Diseases, Clinical Endocrinology, Pediatric Metabolism, and Clinical Hematology.

Arthritis, Bone and Skin Diseases

Rheumatoid Arthritis, Osteoarthritis, Gout

The etiology of rheumatoid arthritis, the most serious and crippling type, is as yet unknown. The hypothesis that it is a disorder of immunity is now widely accepted.

Recent studies have indicated that the chronic inflammation observed in tissues of patients with a disseminated form of rheumatoid arthritis is accompanied by increased immune reactions (with enhanced immunoglobulin levels and rheumatoid factor levels in the blood) and by a drop in serum complement values. Numerous studies in recent years have pointed to the involvement of complement, a protein component of blood, in the body's immunological responses, and to a deficiency of complement in the synovial fluid of some rheumatoid arthritis patients. In the patients studied, complement values were lowest during exacerbations of the joint disease or development of extra-articular complications. The concurrence of low levels of complement with the exacerbations suggests that complement-fixing immune complexes are actively involved in those events.

Discovery of the remarkable anti-inflammatory effects of the steroid hormone cortisone, in 1948, opened a new era in the treatment of rheumatoid arthritis. Continual chemical modifications of the original cortisone molecule have produced drugs that are not only more potent, but also have less tendency to produce serious side effects.

Numerous investigators have reported beneficial results in treating severe cases of rheumatoid arthritis which cannot be checked by conventional therapies with such immunosuppressive drugs as cyclophosphamide and azathioprine. Considerable discussion now centers on use of these drugs, because of their toxic nature and untoward side effects. Investigators emphasize the need to follow certain strict guidelines for their use. These include restricting use to cases with life-threatening complications or potential for serious crippling, where other therapy has been ineffective, and where meticulous follow-up is assured.

The predominant hypothesis to be pursued in future research on rheumatoid arthritis is that it may be due to a pathological local immune response maintained by local antigen-antibody complexes. Initial sensitization is likely to be caused by an initial infectious process. Attention will be directed to alterations of immune mechanisms through immunosuppressive drugs and to control of infection through drugs or vaccines.

Since osteoarthritis is a chronic disease, primarily due to the wear and tear of lifelong usage of the joint involved, drug therapy provides only symptomatic relief. The salicylates, including aspirin, represent the analgesic drugs of choice. They may also have a beneficial effect in retarding additional joint damage.

Gout is a disease entity clinically distinct from other forms of arthritis. Through work done by institute scientists and workers in other institutions the basic metabolic defects causing the disease--increased uric acid production, impaired uric acid excretion by the kidneys, or both--have been elucidated. The mechanism of the highly painful periodic attacks of gouty arthritis is now also understood.

Recently, investigators have reported that purine overproduction and gouty arthritis in some patients can be traced to increased activity of an enzyme of purine metabolism. The researchers describe this distinct abnormality as an indication that disease states may result from genetic alterations leading to increased as well as diminished enzyme function. This is in contrast to most known inborn errors of metabolism, which are based on impairment or lack of a key enzyme.

Treatment of gout centers around the use of two different types of drugs. Colchicine and such drugs as butazolidin are used to overcome the acute attack of pain and joint swelling. Other drugs are used to control the abnormally high uric-acid levels in patients with gout and are given daily as preventive maintenance therapy. Among the latter drugs are the so-called uricosuric agents, which facilitate uric acid excretion by the kidneys, and the drug allopurinol, which has been proved to suppress synthesis of uric acid in the body.

Bone Diseases (Orthopedics)

Research in orthopedics supported by the institute is primarily concerned with disorders of the skeletal system in adults, including all types of injuries to bones, joints, muscles, and associated structures, as well as spinal disorders, infections, tumors, and neuromuscular and metabolic diseases of bones and joints. An important objective of the institute's program in orthopedics is to develop means to prevent complications of arthritic or rheumatic diseases that interfere with joint motion and to develop effective means for relief of these conditions should they occur.

Institute grantees at various centers are continuing to assemble data from extensive trials of total hip replacement employing both new and conventional materials. Among hip joint prostheses, ceramic materials will be compared with man-made polymers and stainless steel. Various types of cements will also be evaluated in these studies, which should eventually point to the optimal procedures in hip replacement and related operations. Use of methyl methacrylate in advanced technique of knee joint replacement has been employed with encouraging results.

Institute support is employed in a multi-clinical survey of the long-term effects of surgical removal of arthritis-impaired joint lining (synovectomy) interfering with joint motion. Until recently, synovectomy, surgical removal of the thickening synovial tissue, was generally used only in advanced cases, but surgeons have demonstrated that synovectomy at an early stage can lead to regrowth, in the same joint, of healthy tissue. Usually this procedure results in reduced inflammation in the joint, with accompanying relief from pain. Further research is needed to determine which patients are likely to benefit from synovectomy and its long-term effects of the surgery on the progression of rheumatoid arthritis.

Osteoporosis is a bone disorder affecting middle-aged and elderly persons, particularly women, which causes a gradual decrease in the amount and strength of bone tissue and leads to many of the fractures in the aged. Treatment, in general, consists of a planned diet rich in calcium and protein, and hormonal therapy, in order to encourage bone mineralization and regeneration. Institute research is centered upon the importance of nutrition in the causation, treatment and prevention. Studies on the effect of various levels of mineral intake and on factors that may interfere with the normal absorption of dietary calcium in the digestive system are receiving special emphasis.

Three topics are of particular concern for the institute's program in orthopedics. The first is comparative clinical trials of total hip replacement. The second is development and testing of novel implantable materials for orthopedic use. The third is an on-going multiclinical survey of the long-term effects of early surgical removal of joint linings (synovectomies) impaired by rheumatoid arthritis.

Skin Diseases (Dermatology)

Dermatologic disorders currently subject to institute-supported research include such disease entities as psoriasis, atopic dermatitis, vitiligo, pemphigus, and discoid lupus erythematosus.

The present state of knowledge in psoriasis may serve as an illustration of the problems currently faced in dermatologic research or practice. The basic etiologic mechanism still remains unknown, but recently, institute-financed epidemiologic studies have shown conclusively that psoriasis is a dominantly inherited disorder. Institute grantees have also provided evidence that disordered metabolism of mucleic acids plays an important role.

In an attempt to accelerate the pace of psoriasis research, the institute has organized workshops bringing together scientists from different disciplines who have pooled their present knowledge and agreed on future research directions. As a result, a collaborative program in clinical trials of topical agents for treatment of psoriasis is planned.

The institute's plans embody an effort to expand the existing base of fundamental knowledge relevant to dermatologic research and to extend clinical studies in this field. In addition to basic studies, scientists will investigate further the use of the potent cytotoxic drug methotrexate, effective in treating severe psoriasis, to learn more about the liver toxicity suspected to be a side effect.

Diabetes, Other Metabolic Diseases and Endocrinology

Diabetes

Diabetes can be divided into two clinical types with different prognoses, somewhat different treatment, and related but possibly dissimilar causal mechanisms. These two types of diabetes are juvenile diabetes and maturity-onset diabetes.

Juvenile diabetes begins during childhood or during the first few decades of life. The disorder progresses rapidly, and most of these patients will eventually develop keto-acidosis with a fatal outcome unless insulin injections are administered regularly. Such patients display greatly accelerated degeneration of blood vessels in many organ systems. This can lead to kidney failure, gangrene in the extremities, heart attacks, and blindness. Even with insulin therapy, the life expectancy of the juvenile diabetic is greatly shortened.

Maturity-onset diabetes, which usually has its clinical start after the age of 40, is generally less severe than that seen in young patients and usually does not progress to keto-acidosis with coma. Accelerated hardening of the smaller arteries, leading to some of the changes described above, does occur in maturity-onset diabetes and results in a decreased life expectancy due to vascular complications. Most patients with this type of diabetes do not require insulin injections, but can maintain their blood glucose at relatively normal levels by controlling their weight, by strict adherence to a low-carbohydrate diet, and by using the oral hypoglycemic drugs. At least 75 percent of all diabetics have the less severe maturity-onset form of the disease.

Recent diabetes research has emphasized studies of a fundamental nature designed to gain a better understanding of the underlying causes of the disease. Studies have been concerned with the question as to whether the small blood vessel disease characteristic of diabetes is the result of an independent primary cause or an effect of long-term diabetes, and the possible role played by human growth hormone. In addition, there are a number of ongoing investigations of new approaches with a therapeutic potential, such as implantation of insulin-producing pancreatic beta cells from normal to diabetic rats. Transplantation of such cells into pockets in the thigh muscles or into the peritoneal cavity resulted in significant reduction of blood and urine sugar levels and restoration of weight gain in the host animals. Although the disease was not cured it was certainly modified and ameliorated. Microscopic studies subsequently revealed intact and functioning pancreatic cells in the transplanted rats, whose native pancreatic beta-cells had been destroyed experimentally, indicating that the animals were utilizing the transplanted cells. Here, too, however, inactivation of the transplanted beta-cells was observed eventually.

Recently, an investigator developed a new approach to the problem of transplanting insulin-producing cells with a greater potential for survival in the recipient patient. He and his associates have maintained pancreatic cultures under laboratory conditions for periods of up to ten days. They showed that beta-cells, grown in these cultures, are capable of synthesizing insulin and that the cells respond to high glucose levels by releasing extra insulin. They also showed in the diabetic rat that a single transplant of functioning beta-cells was effective in controling all symptoms of diabetes for more than one year.

In the meantime, surgeons have transplanted the entire pancreas into diabetic patients who were subsequently treated with immuno-suppressive drugs. The transplanted organs were capable of secreting insulin for a number of weeks and the diabetes was improved temporarily. Although whole pancreatic transplants may not prove to be a very practical solution to the diabetic problem, because of the limited number of usable donors likely to be available, the experiments have furthered our understanding. To date, however, transplants of the entire pancreas have, on the whole, not survived more than one year.

A primary goal in institute diabetes research is to understand the basic impairment of insulin activity, a complete knowledge of which would uncover some of the riddles now surrounding the disease. Studies will center on the physiology of insulin, and will seek to establish how this hormone exerts its influence on cell membranes and, consequently, cell metabolism. In the clinical area, institute scientists will study patients with assays of plasma insulin and measurements of basement membrane thickness in various tissues. A new mode of therapy showing some degree of promise--administration of insulin through aerosol inhalation--will receive continued support. A further evaluation of the efficacy and safety of the oral anti-diabetic drugs will be made.

The use of high carbohydrate diets in patients with mild diabetes will also be studied. Preliminary investigations have demonstrated that oral glucose tolerance improves significantly with periods of relatively high carbohydrate feeding.

These programs will be greatly enhanced through the recent creation of a Diabetes Branch within intramural research, the establishment of grants to establish four Diabetes-Endocrinology Centers to expedite the flow of new scientific information, and the passage of the National Diabetes Millitus Research and Education Act of 1974 (Public Law 93-354) which calls for a long-range plan of attack on diabetes, primarily in the areas of research, development of new techniques of community level treatment and public education, and professional training.

Other Inherited Disease of Metabolism

Recognition of the other hereditary metabolic diseases, as well as understanding of the mechanisms by which they produce discomfort and dysfunction, has increased immensely over the past half century, Further emphasis needs to be placed on early recognition of these "inborn errors of metabolism," inasmuch as early detection and improved medical management can delay the onset of complications and, in some instances, permit a longer survival. Institute and institute-supported scientists have been particularly productive this past year in their studies of this group of diseases, one of which is cystic fibrosis (CF).

Institute scientists and grantees have developed reliable and accurate diagnostic tests based on the salt content of sweat, fingernails and hair. A recently simplified method allows this determination to be performed on an infant prior to discharge from the hospital nursery. Anabolic steroid hormone therapy and antimicrobial agents to fight lung infections have been introduced by institute grantees.

Studies of still another metabolic disorder, Wilson's disease, are expected to continue to produce results. Wilson's disease is a familial syndrome of progressive neurologic and hepatic disease caused by faulty copper metabolism and abnormal copper accumulation in body tissues. The use of potassium sulfide to prevent dietary copper absorption and of penicillamine to increase urinary copper excretion is well documented, and reports concerning successful control of the disease through such long-term therapy have been presented by grantees.

Treatment of Wilson's disease with penicillamine for 9 to 13 years has resulted in maintenance or restoration of normal liver function, disappearance of neurologic manifestations, and disappearance or marked fading of characteristic corneal pigmentation in all patients so treated. These and other observations have provided some insight into the natural history and pathogenesis of Wilson's disease, and testify to the efficacy of this regimen.

One of the most attractive therapeutic procedures for diseases due to hereditary enzyme deficiency is induction or replacement of enzyme activity (as in treating Fabry's disease). There is also opportunity for progress in dealing with the diseases of genetic origin through a systematic study of deranged metabolic processes. It is estimated that between 50 and 100 different inherited metabolic defects, most of them unknown at this time, will be elucidated if such studies are undertaken on a larger scale. There is need for further investigation of the basic chemistry of DNA and RNA, the complex nucleic acids that occupy central roles in the transmission of genetic information from cell to cell and generation to generation. And this and other approaches will lead to much-needed knowledge of problems. in general. With the aid of such additional knowledge, it may eventually be possible to modify the genetic constitution of individuals with hereditary metabolic diseases.

Immediate plans involve efforts to extend fundamental studies of genetic material proper, including studies of chromosome structure in man, and of genetic control of protein and enzyme synthesis and regulation. The institute anticipates a broadening of ongoing clinical investigations and therapeutic trials in metabolic disorders.

Metabolic and Endocrine Disorders (Unrelated to Genetics)

Most of the extremely important work throughout the world which has led to the development of oral contraceptives is based on endocrinologic studies. Several institutes of NIH maintain active programs in the field of endocrinology as it pertains to their specific areas of responsibility. NIAMDD supports the bulk of the basic endocrinology research. In addition, studies concern a host of diseases including hypo/hyper/thyroidisms, hypo/hyper/parathyroidisms, rickets, osteomalacia, vitamin D-resistant rickets, osteoporosis, growth retardation, Cushing's syndrome, and Addison's disease.

The recent development of a highly sensitive radioimmunoassay for parathyroid hormone is expected to improve diagnostic accuracy for hypo- or hyper-parathyroid states and to allow measurement of rates of secretion of the hormone. Patients with hypercalcemia, hypophosphatemia, nephrocalcinosis, nephrolithiasis, or other manifestations of hyperparathyroidism will be examined for the effects of calcium or EDTA infusions or dietary phosphate on the secretion of parathyroid hormone.

Attention will also be given to renal and gastrointestinal responses to the effects of the hormone. These studies will include work on selected cases of hypoparathyroidism, rickets, osteomalacia, vitamin D-resistant rickets, osteoporosis, and certain other abnormalities of bone metabolism.

Strides have been made in knowledge of the molecular structure and in the laboratory synthesis of specific hormones. After 32 years of research, human pituitary growth hormone (HGH), previously isolated and identified by an institute grantee, has been synthesized by the same scientist. Relatively pure preparations of human pituitary growth hormone now permit children afflicted by hypopituitary dwarfism to attain a satisfactory measure of growth, although an extremely limited natural supply means that a final solution will depend upon successful inexpensive, large-scale chemical synthesis, or chemical modification of an animal growth hormone.

Another important basic finding by an intramural scientist and an institute grantee resulted in successful synthesis of the active portion of parathyroid hormone and discovery of the precise mechanisms through which it controls calcium metabolism in the body. The synthesis will have important implications both for better understanding of the biochemical operation of other hormones and for improved diagnosis and treatment of a number of human disorders, including hyperparathyroidism, kidney stones, and metabolic bone diseases.

With the multiplicity of objectives in this field, the approaches are also widely diverse. To assist the work of investigators in endocrinology, the institute maintains a hormone development and distribution program. This consists now of several contract operations and will be expanded in the future. One operation under way is that of the National Pituitary Agency, whose aim is to improve the collection of human pituitary glands and to provide for distribution of purified human growth hormone and other materials to qualified basic and clinical investigators. Another contract provides for distribution of purified rat pituitary hormones and purified cholecalciferol metabolites to qualified research workers.

Digestive Diseases and Nutrition

Gallbladder Disease and Gallstones, Peptic Ulcer, Ulcerative Colitis, and Other Disorders

The institute has recently expanded its clinical and laboratory investigations to determine abnormalities in structure and function of the esophagus, stomach, small and large intestines, pancreas and liver, and its research on certain hereditary metabolic diseases. It has also initiated investigations of gallbladder disease at the Indian Health Service's modern five-story Phoenix Indian Medical Center.

NIAMDD scientists who had shown that the Pima Indians of Arizona have a rate of gallbladder disease six times higher than that found in Caucasians in Framingham, Massachusetts, are now attempting to associate this high rate with possible predisposing conditions, such as pregnancies, body weight, and diabetes. Recent progress in the study of bile acid metabolism and biliary cholesterol secretion has been rapid. The primary thrust of current investigations is toward nonsurgical approaches to the prevention and treatment of gallstone disease.

About two years ago investigators reported that long-term oral administration of chenodeoxycholic acid (a natural bile acid) can result in dissolution of long-standing cholesterol gallstones. More recently, an initial contract was awarded to Cedars-Sinai Medical Center in Los Angeles to supervise and participate in a long-term collaborative clinical study of the feasibility, effectiveness and safety of dissolving gallstones with the aid of chenodeoxycholic acid. This is the first comprehensive study undertaken to determine the efficacy of a medication for gallstone dissolution and, through ancillary research, to find out how gallstones form and what causes their formation.

Some of the most exciting research in peptic ulcer revolves around gastrin, the hormone which stimulates secretion of gastric juices. The synthesis of gastrin accomplished in previous years has provided an important tool for studying peptic ulcer, in which an excess of acid digestive juices is secreted. Since then, other investigators have shown in rats that experimental induction of immune antibodies against gastrin can inhibit the potent gastric acid stimulatory action of gastrin. This suggests possible novel approaches to counteracting excessive gastric acid secretion in human disease states such as peptic ulcer.

Other research involves histamine, well known to allergists as part of the immune defense mechanism, which can dilate capillaries, stimulate smooth muscle, precipitate hives and induce other inflammatory and allergic reactions. It also stimulates secretion of gastric acid in the stomach. Conventional antihistamine drugs are incapable of counteracting this gastric acid secretion, but recently a British team has been successful in developing a new drug, Metiamide, which can block the effect of histamine of the heart, the uterus and the stomach, and can thus mitigate histamine's enhancement of gastric acid secretion.

Progress has been made in the development of new methods of therapy for ulcerative colitis. Although the disease responds to oral corticosteroid drugs, undesirable side effects, including growth retardation, result from the continuous large doses that are required to be effective. The development of topical steroid drug treatment in the form of enemas has eliminated undesirable side effects to a significant degree.

As part of the institute's plan to intensify program efforts in the area of digestive diseases, a new collaborative research project, the National Cooperative Crohn's Disease Study, has been initiated. This study is designed to determine the efficacy of several commonly used regimens in the treatment of regional ileitis (Crohn's disease). The study, initially involving eight university medical centers, will be a controlled, randomized clinical evaluation of three currently used drugs, prednisone, Azulfidine and azathioprine, to determine the effectiveness of these agents. The study will examine each drug's effectiveness in preventing intensification and recurrence of the disease.

Nutrition

The nutrition research grants program of the institute may be divided into two major groupings: physiology of normal nutrition and nutritional disorders. Projects in the physiologic processes of normal nutrition involve body composition, digestion and absorption of nutrients in the gastrointestinal tract; appetite regulation and food intake; the biochemistry and physiologic role of nutrients and their fate in the body; quantitative requirements of proteins, amino acids, carbohydrates, fats, fatty acids, minerals, trace elements, vitamins, and fluids and electrolytes; interrelations between different nutrients, nutrients and hormones, and nutrients and enzymes; and the relationship of the intestinal flora to nutrition.

Research in abnormal nutrition involves obesity, malabsorption of specific nutrients, discovery and definition of deficiency states, nutrient toxicity, and the relationship of diet to specific disease entities, such as cystic fibrosis, celiac disease, and sprue. Another major subdivision relates to nutrition in specific diseases or stress states such as diabetes, bone and joint disease, liver disease, infectious disease, inborn errors of metabolism, skin disorders, kidney disease and stress (including pregnancy, surgery, trauma, wound healing, and environmental extremes). Parenteral nutrition (administration of nutrients intravenously) is becoming increasingly important in the management of chronic diarrheas of malnourished infants and in a great variety of gastrointestinal dysfunctions and postsurgical states. The real basis for these newer approaches in hyperalimentation rests upon much fundamental research on man's nutritive requirements over many years--research supported in large part by the institute.

Clarification of how vitamin D affects production of a calcium binding protein, and how this protein, in turn, aids intestinal calcium absorption, is one example of an outstanding study that has continued for the past several years.

Vitamin D acts to maintain normal bone mineralization and metabolism by facilitating and regulating the absorption of calcium and phosphorus from the intestinal tract. About 2 years ago, a major biologically active form of this vitamin, 25-hydroxycholecalciferol, or 25-HCC, was isolated from plasma by a grantee scientist at the University of Wisconsin. He subsequently showed that vitamin D is converted to 25-HCC in the liver, and that the metabolite may be a safe and effective form of therapy for vitamin D-resistant rickets.

Almost simultaneously, he and two other grantee investigators at other institutions now have obtained evidence to indicate that 25-HCC is converted in kidney tissue to a still more active form of vitamin D, namely 1,25-dihydroxycholecalciferol. The newly described metabolite may represent the ultimate biologically active form of vitamin D in the intestine. It is more than twice as active as 25-HCC in stimulating.

This finding should afford several new avenues of experimentation. It should now be possible to synthesize the new metabolite, to determine its precise mode of action and its relationship to other known regulators of calcium metabolism, and to determine its efficacy in the treatment of several diseases resulting from abnormal vitamin D metabolism.

For the last several years research in obesity has focused on treatment, effects of exercise and fasting regimens, and fat cell activity. Obesity affects directly or indirectly a number of disorders such as hypertension and atherosclerosis, hernia and gallbladder disorders, diabetes, and several other chronic diseases. Obesity is one of the most important problems in the United States today, inasmuch as 20 percent of all adults are overweight to a degree that impairs their health and longevity.

Evidence continues to accumulate which links the adult form of diabetes to obesity in those persons predisposed to the disease by inheritance. It is known that large fat cells are more refractory to insulin than small ones. Institute-supported scientists recently found that experimentally induced obesity in adult humans is achieved primarily by an increase in adipose cell size without a change in adipose cell number. This may explain the relative insensitivity to insulin, and the consequent metabolic aberrations, which accompany obesity--particularly in individuals genetically predisposed to diabetes.

Studies on the morphogenesis of adipose tissue cells will be continuing, but they should be accompanied by research on psychogenic, hereditary and other factors regulating appetite, on endocrine and metabolic dysfunctions, on specific effects of individual nutrients, on overall dietary composition, on body composition, and on the value of gastrointestinal short-circuiting as a treatment of extreme and intractable obesity.

Another research area that will continue to be pursued in the future is that involving studies of vitamin D, its metabolites, their relationship to stimulation of intestinal "calcium-binding-protein" production, the determination of how this protein aids intestinal calcium absorption, and other investigations involving bone mineralization and calcium and phosphorus metabolism.

Some subjects of further studies will be interrelations between carbohydrate, fat and protein metabolism; the effects of diet on body composition; and the factors of appetite regulation.

Kidney, Urologic and Blood Diseases

Glomerulonephritis, Nephrosis, Urinary Tract Stones

Kidney diseases may be classified as follows: (1) hypersensitivity diseases, in which kidney tissue is destroyed by an immune reaction initiated by several causes, including hypersensitization during a previous streptococcal infection; (2) infections, in which kidney tissue is attacked and destroyed by microorganisms; (3) circulatory diseases, in which the kidney is affected as a result of disease of the blood vessels; (4) metabolic diseases, in which the kidney is secondarily affected, as in diabetes or gout; (5) developmental disorders in which the kidneys fail to develop in a normal fashion; and (6) obstructive conditions, in which urine flow is blocked, resulting in pressure damage to the kidney and repeated infections.

Glomerulonephritis (Bright's disease) is a common disorder characterized by an inflammatory reaction in the kidney glomerulus, causing leakage of blood and blood constituents into the urine, and by alteration of many of the filtering functions of the kidney. Most cases of the disorder are self-limited and, after a period of weeks or months, heal and leave no residual damage, but in a certain percentage damage is progressive, leading to a uremic death. The disease follows certain streptococcal infections in other parts of the body. The streptococcus is believed to alter the body's normal immune responses, precipitating a local abnormal immune response with damage to the kidneys. A new collaborative program to begin soon is a multiclinical study of the efficacy of immunosuppressive and other drugs in the treatment of glomerulonephritis and other chronic immunologic glomerular diseases.

Nephrosis (idiopathic nephrosis) is a disorder of kidney tubules which leads to a characteristic disturbance in body metabolism, with loss of protein into the urine, resulting in low levels of blood protein and generalized fluid retention and body swelling (edema). Corticosteroid drugs have greatly reduced the death rate and have lessened the severity of the condition. The drug azathioprine (an immunosuppressive agent) has been tried in corticosteroid-drug-resistant patients with encouraging results. The investigators conclude that azathioprine merits further trials in patients with the nephrotic syndrome, especially preadolescents with growth retardation secondary to corticosteroid therapy, or in other patients for whom steroid treatment is contraindicated.

It is hoped that biomedical science will ultimately be successful in developing new and effective methods of tissue matching and organ storage, and thus make possible the use of kidney transplantation as a standard and permanent therapeutic measure. But even if such success is achieved, it should be noted that transplantation depends upon hemodialysis (use of artificial kidneys) until the kidney-failure patient is ready for an operation and until a suitable donor kidney is available. Dialysis is also used post-operatively as a temporary kidney-sparing measure and, in the case of transplant failure, as a life-saving maintenance method.

Transplant rejection is still the most important factor preventing kidney transplantation from being used with predictable results routinely on a large scale to resolve systematically the problem of the patient in end-stage kidney disease. The problem of organ preservation, essential in the case of cadaver kidneys for proper matching of the organ with a suitable recipient and the logistics of reaching the out-of-town recipient patient, has been advanced toward solution during the last few years, but improvements in preservation methods are still needed.

Although artificial kidneys have been known for over two decades, and have been used in cases of poisoning or acute kidney failure, repeated use of these devices in any one patient was limited. Institute-supported development of permanently implanted, connected plastic tubes in an artery and vein of the forearm, providing an indwelling shunt, has started a new era of hemodialysis in patients with permanently impaired kidney function. Repeated use of artificial kidneys in such patients on a thrice weekly schedule now permits the saving of lives that would otherwise be lost because of inevitable fatal uremia.

An important event has been the revision of the Social Security law to provide financial assistance to patients with irreversible kidney failure. This Medicare provision provides payment of dialysis treatment or kidney transplantation to all end-stage disease patients covered by Social Security, or their dependents. It is expected that this will result in a population of patients on maintenance dialysis numbering 40,000-50,000 within the next few years.

As the life-extending potential of artificial kidneys became apparent nine years ago, the Institute's special Artificial Kidney-Chronic Uremia Program was created to expedite research and development in this field.

Consultants advise that fundamental research on the nature of uremia must proceed side-by-side with efforts to improve dialysis apparatus and techniques. Thus, studies on the metabolic characteristics of kidney failure and on its largely unknown toxic products are fundamental to rational design of a more effective dialysis machine or device, and for the initiation of a productive program of applied research and development for simpler, more economical, and more efficient dialysis.

The high hospital overhead, the limited functional life of apparatus, and the need for costly professional personnel are primarily responsible for the current high cost of dialysis, which averages $32,000 per patient per year in hospitals. Home dialysis, in contrast costs from $3,500 to $7,000 per year after the initial outlay for training and equipment.

At present about 70 research and development projects are supported by contracts with universities, nonprofit and industrial research laboratories to give a broad approach to problems of highest priority. Projects are focused on problem areas including clinical trials of more efficient or less costly dialyzers, development of special adsorbents for uremic toxins, studies to elucidate the nature of the aberrant metabolic changes in uremia, and the maintenance of a national registry of all patients who are being maintained with the aid of dialysis. The program is also funding studies armed at isolation and identification of toxic factors which must be removed from the patient's blood, in addition to metabolic wastes and other substances known to accumulate during kidney failure. A large number of research projects is also devoted to the pathophysiology of uremia in an effort to prevent or control complications in patients who have lost their kidney function and are being maintained with the aid of artificial kidneys.

Hematology

New initiatives and research are forthcoming in the area of Cooley's anemia following passage of the National Cooley's Anemia Control Act, which provides for expanded programs of research, diagnosis, prevention and treatment of this disorder, an inherited blood disease which occurs primarily in persons of Mediterranean ancestry. In the United States most of the victims are of Italian, Greek, Turkish, French or North African descent, although the disease is not limited to these groups.

No cure is known, and the only effective treatment is administration of blood transfusions, usually once a month, but sometimes more frequently, to alleviate the constantly recurring anemia. A serious complication is a progressive overload of iron in the body resulting from frequent transfusions. There are agents with limited effectiveness in removing the excess iron, but those now available are too toxic for general use.

A steady advance has occurred in our knowledge of blood diseases, much of it during the past decade. Diagnostic techniques in the various blood diseases have become highly developed, and accurate diagnosis is frequently the key to successful treatment. Institute-supported research has contributed much to current knowledge of the molecular structure of hemoglobin and of the disordered amino acid sequence in abnormal hemoglobins. Substantial advances have been made recently in the physical chemistry of blood-clotting mechanisms and in the understanding of bleeding disorders.

Institute scientists have shown that infusion of an antihemophilic-factor concentrate is an effective therapeutic agent for hemophilic patients undergoing surgery who would otherwise run the risk of uncontrollable bleeding. One institute-supported scientist has used potent concentrates of antihemophilic globulin derived from animal sources to control life-threatening hemorrhages in patients with circulating antibodies to the human coagulating factor AHG (antihemophilic globulin).

The availability of concentrated, though expensive, coagulation factors VIII and IX has reduced the risk of surgical procedures in patients with hemophilia A and B to normal levels. Several investigators, in reporting their experiences with the successful use of these concentrates during surgery in hemophilic patients, recommended recently that such therapy need not be continued for longer than 2 to 4 weeks postoperatively.

One of the most important stimuli in hematology research is the continuing need for defining the metabolic mechanisms responsible for anemia. Hemoglobinopathies, mineral, vitamin, hormone and enzyme deficiencies, hemolysis due to pathologic immune mechanisms, and drug sensitivity--the major etiologic entities involved in anemias--will all be under intensive investigation.

Hemoglobin variants of animals and man will be studied and the exact structure and composition of their molecules defined. Drawing on this biochemical background, studies will continue on the structural-functional relationships of abnormal hemoglobins producing such human diseases as thalassemia and other hereditary hemoglobinopathies.

Special Activities

Scientific Communications

A continuing problem confronting individual physicians and research scientists today is the difficulty of keeping up with rapidly developing fields of knowledge directly or indirectly related to their work. The institute, through its Office of Scientific Communications, will continue to provide current-awareness("alerting") publications amd other similar materials in areas within its purview, conduct retrospective literature searches, initiate conferences and workshops, and publish their proceedings in order to provide the widest possible dissemination of up-to-date research information. The institute will also conduct other activities related to scientific communication, such as the production of a limited number of specialized motion pictures and development of thesauri in carefully selected areas where the state of knowledge is less than optimal.

The institute now issues on a regular basis five current-awareness publications in major disease areas important to its mission. Currently published on a monthly basis are Diabetes Literature Index and Gastroenterology Abstracts and Citations. In addition, Endocrinology Index is published on a bimonthly basis and Artificial Kidney Bibliography on a quarterly basis. The latter, currently being expanded, will eventually become the Kidney Disease and Nephrology Index. The newest and fifth publication, the Index of Dermatology, is published on a monthly basis.

Each of these publications covers the entire scientific literature related to the subject matter (diabetes, gastroenterology, etc.) from throughout the world regardless of the original language. The response by investigators and medical school staffs has been enthusiastic, and the need and usefulness of the publications have been clearly documented.

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NATIONAL CANCER INSTITUTE

Identification of the Problem

"Cancer" is a term applied to more than 100 clinically distinct diseases that kill someone in the United States every one-and-a-half minutes. In 1974 an estimated 655,000 Americans will become new cancer cases, 1,310,000 will be cancer patients, and 355,000 will die of cancer. The annual cost of cancer is about $20 billion. The incalculable suffering of victims, their friends and families is of course unmeasurable.

In the early 1900's few cancer patients had any hope of cure. The five-year survival rate in the late 1930's was about 1 in 5. Ten years later it was 1 in 4 and today the figure is about 1 in 3. This means that roughly 55,000 patients are being saved each year. The immediate goal of cancer control in this country is to save 321,000 lives a year, or half of those who develop cancer. On the basis of five-year survival, about 224,000 Americans will be saved from cancer this year. About 1.5 million Americans are alive and free of cancer five years after treatment. An additional 1 million cancer patients diagnosed and treated within the last five years will live to join these ranks.

The National Cancer Program

Since its creation in 1937, the National Cancer Institute has been the primary agency through which the Federal Government has sought to marshal biomedical research toward the goal of controlling cancer. The activities of the Institute have been directed toward providing, through research, improved means for the prevention and diagnosis of cancers in man, and the cure and rehabilitation of those cancers that have not been prevented.

The National Cancer Act of 1971 rested on the conviction that medical and scientific understanding of cancer had reached a level where sustained pursuit of new scientific leads could advance national capacities to prevent, diagnose and treat cancer. The Act stipulated that an intensified and coordinated national program would be needed to quicken the pace for developing the means to bring cancer under control.

The National Cancer Act gives the National Cancer Institute the responsibility for organizing this complex undertaking and for channeling the resources needed. The Act requires the Director of the Institute to "plan and develop an expanded, intensified, and coordinated cancer research program encompassing the programs of the National Cancer Institute, related programs of the research institutes, and other Federal and non-Federal programs." This mandate includes support for cancer research in industry and in other countries outside the U.S.

To speed the translation of research results into widespread applications, the Act directs the establishment of a Cancer Control Program to demonstrate to both the medical community and general public the applications of the latest advances in cancer prevention and control. In the additional approach to the same problem, the Act directs the establishment of 15 comprehensive cancer centers combining research, training and demonstration.

An overall strategy for the National Cancer Program has been developed, based on a consensus among Federal and non-Federal clinicians and laboratory scientists about the direction, content and pace of the research program. The strategy and plan for the national program will be revised regularly as new information and concepts flow from the laboratory and clinic. The strategy involves the systematic sharing of cancer information by public and private agencies throughout this country and abroad. It requires continued assessment of resource needs and logistical planning to meet those needs. In some cases, it necessitates the redeployment of existing facilities, the rapid evolution of new kinds and combinations of research support, the reassignment of science management responsibilities, and the development of new mechanisms of technological transfer and information retrieval and application.

In 1974, the National Cancer Act of 1971 was amended to provide a more comprehensive National Cancer Program. Modifications in the provisions and increased funding was authorized to improve the capability of the National Cancer Program to pursue its twin objectives of producing new knowledge through research and encouraging the widespread application of knowledge to save lives.

NCI Approaches to Research

Research supported by the National Cancer Institute is organized into the broad areas of cancer biology and immunology; cause and prevention; detection and diagnosis; and treatment and rehabilitation. This broad spectrum of research is conducted through five Divisions of NCI: Cancer Biology and Diagnosis; Cancer Cause and Prevention; Cancer Treatment; Cancer Research Resources and Centers; and Cancer Control and Rehabilitation. NCI intramural research is conducted in NCI laboratories in Bethesda, Maryland, and at the NIH Clinical Center, Bethesda; the Veterans Administration Hospital, Washington, D.C.; Baltimore Cancer Research Center, Baltimore, Maryland; and the Frederick Cancer Research Center, Frederick, Maryland.

Cancer Biology

The cancer biology program is focused on the transformation of normal cells into cancerous ones, and on factors affecting the growth of cancer cells. The research encompasses aspects of cell biology, molecular biology, genetics and tumor biology. These and other basic science areas relevant to cancer may range beyond the narrowest boundaries of cancer research, but they are all vitally related to cancer. Such fundamental studies are necessary for the development of better methods of preventing, diagnosing and treating this group of diseases.

Research in cancer biology also includes basic laboratory studies of how cancer-causing agents, such as viruses, interact with cell components to cause cell transformation. Related studies are concerned with how these processes may be altered to prevent cancer and how these processes might be used for cancer diagnosis or treatment.

It has been difficult to isolate viruses from cancer cells, especially from human cancers, but scientists at the Institute and in other laboratories of the National Institutes of Health have found that certain chemicals can cause cells to reveal viruses not otherwise detectable. Specific enzymes have been found which promote the insertion and removal of virus genes, the biologic units of heredity. The fundamental process of interaction of host cells and viral genes, which may hold important answers about both cancer causes and possible methods of treatment, is under intensive study.

A major recent advance focuses on certain animal cancers caused by viruses of the ribonucleic acid (RNA) type, which contain the enzyme reverse transcriptase. This enzyme allows the genetic information of this type of virus to cause a permanent and cancerous change in the genetic make-up of infected cells. The same enzyme has been found in some human cancer cells, supporting the belief that such cancers are induced by blocking the action of the enzyme.

Other studies have shown that two types of mouse mammary tumor virus exist, one that is transmitted to offspring in milk as might occur with an infectious virus, and one transmitted only within the fertilized egg as a genetic inheritance. A specific mouse gene that predisposes to mammary cancer has been localized. Work is under way to determine if this gene may be the virus itself, incorporated into the cell.

The actual insertion of virus into genes and its later removal is under study in a much simpler system of a bacterium and a bacterial virus. It has been shown that a gene-directed process, and presumable the gene itself, can be transferred between cells of two species of animals. New techniques developed by other Institute scientists permit the observation of alterations in genetic material from animal cells transformed by cancer-causing chemicals.

In studies of cells grown in the laboratory, work is in progress to identify changes in cell metabolism that accompany malignant transformation. A number of abnormal properties of transformed cells seem to be related to their inability to accumulate a chemical compound, cyclic adenosine monophosphate, that facilitates normal intracellular processes. Another important chemical characteristic of cancer cells may be a factor isolated from some cancers that induces rapid growth of blood capillaries supplying the tumor. It is thought that this factor must be present before the tumor can grow larger than a few millimeters in size.

Studies of cancer cells under experimental, laboratory conditions may be made more directly relevant to cells in living systems through use of an artificial circulatory network that permits living cells to be grown to a density that resembles natural body tissue. The laboratory device simulated the conditions of living tissue by growing cells inside a glass shell fitted with a bundle of tiny tubes through which a nutrient fluid, comparable to blood, is continuously pumped. In one use of this system, investigators are varying hormones and other ingredients in the nutrient fluid, in order to study conditions that promote or inhibit growth of cancer tissue.

Research concerned with differences in the surface membranes of cancerous and normal cells is being aided by electron microscopy, which uses electron beams instead of light to make highly-magnified images. Antigens, substances which initiate the body's immune response, can be visualized on cell surfaces with the aid of the electron microscope and fluorescent antibodies, which react specifically with antigens. Antigens visualized on the surfaces of some cancerous animal cells appear to be specifically related to a number of viruses that cause cancer in animals. Further studies may help define a possible role for viruses in human cancer, or may lead to isolation of surface antigens for use in diagnosis and treatment.

Immunology

Recent years have seen the very rapid development of the science of immunology, which is concerned with highly specific chemical substances, or antigens, produced by cells and with their interaction with equally specific antagonists, or antibodies, produced by other cells. Immune reactions of antigens and antibodies provide the body's major defense of its integrity, either against external invaders such as bacteria and viruses or, as has been recognized recently, against internal invaders, namely cancer cells. Experimental and clinical observations have led to the hypothesis that cancer as a disease is a consequence of failure of the immune defense mechanisms. How the immune system recognizes cancer cells as abnormal has become a central focus of cancer research.

The growing importance of immunology research has led to development of a major Institute program in cancer immunology. This program supports efforts almost equally divided among (a) basic studies of the immunologic aspects of cell transformation and cancer growth; (b) the diagnosis of cancer by immunologic means; and (c) the immune therapy of cancer.

A major effort in basic cancer immunology is concerned with the identification and characterization of cell surface antigens of both normal and cancerous cells, including antigens induced by cancer viruses and antigens specific to tumor types. Procedures are being developed to isolate antigens without destroying their activity. Perfection of these procedures will greatly facilitate a planned approach to immunodiagnosis and immunotherapy.

Other studies are directed toward understanding the components of the immune defense system. Antigens and antibodies may be either humoral--that is, secreted into the body fluids of "humors"; or cellular--that is, an integral part of cell surfaces. The cells of the immune system are the white blood cells, including macrophages and lymphocytes. Scientists have learned that lymphocytes can function as either humoral or cellular immune agents. Lymphocytes in the humoral system can be identified by their capability for reacting with a specific type of antibody. This same antibody type appears to help destroy foreign cells by coating them and thus identifying them for attack by other cells of the immune system.

Further understanding of the immune system has come from studies with patients who have immune deficiency diseases. Patients with these rare and often inherited disorders have a higher than normal susceptibility to cancer, an observation which is part of the evidence linking cancer with failure of the immune system. Scientists have found that the immune disorders can be traced to defects in different components of the immune system. Patients with ataxia talangiectasis have a limited ability to make antibodies and lymphocytes. Patients with the Wiskott-Aldrich syndrome, on the other hand, produce normal amounts of antibodies and lymphocytes but have a defect in recognizing antigens and responding to them. In a third type of defect, patients with intestinal lymphangiectasis lose body fluid into the stomach and intestine, carrying with it dissolved protein and lymphocytes, particularly lymphocytes of the cellular immune system.

Detection and diagnosis of cancer is being aided by immunology research in a number of ways. Investigators have shown that certain forms of cancer have characteristic, identifying antigens. Such tumor-specific antigens are being sought for additional cancers. Several studies are concerned with one or more antigens associated with acute leukemia, Hodgkin's disease and non-Hodgkin's lymphomas.

Cancers may also be identified by immunologic detection of products of cancer-cell metabolism. Several of these products have antigens that are found also with fetal or emryonic cells. Two of these products in particular, carcinoembryonic antigen and alpha-fetoprotein, are the subjects of research directed toward their detection, isolation, and relationship with several types of cancer.

Other antigens associated with cancer are also associated with viruses. Scientists in several laboratories are exploring the relationship between a herpesvirus and a number of cancers, including cancer of the cervix. These studies may increase the understanding of the role of viruses in cancer causation, but they are also important for providing potential immunologic "markers" for cancer.

Investigators are exploring the use of cancer-associated antigens in tests for the presence of cancer cells, both before cancer may be detected by other means and after treatment. Preliminary clinical studies show particular promise in the latter area, the use of immunologic tests to monitor the progress of treatment. Investigators studying several kinds of cancer have found that the amount of cancer-associated antigen in a patient's blood will decrease after removal or destruction of cancer cells. The antigen level may rise again if cancer cells remain and resume their spread.

Research on the immune therapy of cancer largely involves exploratory studies with animal models, although some carefully controlled work in human patients is in progress. The long-term goals of immunotherapy are to enhance a patient's immunity to cancer, or to produce specific antisera that on injection will destroy cancer.

Cancers are in some way protected from the expected rejection by the body, rejection that the foreign cancer antigens should trigger. One hypothesis is that, in response to a patient's tumor, a "blocking antibody" is produced, stopping the action of the patient's natural defense system. Blood samples from some other individuals seem to be able to partially deblock the "blocking antibody". To explore this possibility, studies are in progress in patients with far-advanced neuroblastoma, a cancer of the nervous system, and malignant melanoma, a rare but often fatal cancer of the skin. An effort is being made to enhance these patients' immunity by injection of deblocking blood serum while at the same time boosting their defense system by injection of the patients' own cancer cells.

In a somewhat different approach, patients with far-advanced cancers are being injected with their own cancer cells which have been treated with the enzyme neuraminidase. The hypothesis is that cancer cells growing actively in a patient are coated with proteins that reduce the cells' ability to cause immune rejection. Removal of the coating may promote antigenicity and lead to immune destruction of the cancer.

BCG (bacillus Calmette-Guerin, a strain of bacteria) is a tuberculosis vaccine that is being evaluated in cancer treatment. BCG is believed to act by stimulating the body's immune defense system to attack cancer cells. In research with guinea pigs, scientists have found that injection of BCG can reverse the growth of established tumors that have begun to spread beyond their original sites. Results have been reported in only a small number of patients and thus far are equivocal. Further studies are needed to establish the effectiveness of this approach to cancer treatment.

Because of the growing number of studies applying immunologic methods to cancer treatment, the Institute has established an International Tumor Immunotherapy Registry to serve as a worldwide center for information on clinical trials. The Registry collects and distributes reports on the progress of current studies of immunotherapy. The exchange of information is intended to prevent duplication of unsuccessful treatments and encourage cooperation in studies of promising approaches.

Additional research in biology and immunology will be performed during FY 1975 on exploration of differences between normal cells and tumor cells to increase the immunologic defenses of individuals against tumor growth; research on the immune responses to tumor viruses; and studies advancing knowledge in molecular and cell biology of the malignant process.

Cause and Prevention

The national program for the identification of the causes of cancer and for its prevention covers three broad areas: epidemiologic studies to identify situations where cancer is prevalent and to detect possible clues to causative factors, studies on chemical and physical carcinogens, and studies on viruses that may cause cancer.

Fortunately, based on a combination of epidemiologic and laboratory studies, important progress is being made in finding causative processes and in developing screening tests to identify individuals who have a higher than average risk of developing various types of cancer. However, new knowledge is not even required in some instances to make progress in reducing deaths from cancer. Estimates have been made that information already in hand, if applied, could save 100,000 lives over the next five years.

The Institute is conducting several important epidemiologic studies on cancer. They include: (1) a series of industrial studies; (2) studies involving migrant populations to the United States and their relatives abroad, focusing on factors related to the incidence of colon cancer; (3) the Third National Cancer Survey, the largest single study ever done on the incidence and prevalence of cancer in this country; (4) a county-by-county analysis of deaths due to 35 types of cancer in the United States over 20 years; and (5) a newly developed system to monitor trends in cancer incidence.

In the industrial studies excesses of cancer incidence were found in steelworkers, smelter refinery workers, and uranium miners. In view of the importance of industrial exposures as a source of cancer, the program has become more heavily involved in industrial epidemiology, in cooperation with the National Institute for Occupational Safety and Health, the Environmental Protection Agency, and other Government agencies.

Studies in Hawaii (in cooperation with the Heart and Lung Institute) have provided a very strong suggestion that meat--in particular beef--is associated with the four-fold increase in cancer of the large bowel in Hawaiian Japanese. This work is being followed up in the search for bacterial flora possibly capable of producing carcinogens in the lower bowel.

The Third National Cancer Survey, still being analyzed, provides incidence and prevalence data for the years 1969 through 1971 for seven metropolitan areas, two entire states, and the Commonwealth of Puerto Rico. Making the necessary statistical adjustments and excluding common skin cancers, the Survey findings indicate that approximately 610,000 new cancers were diagnosed in this country in 1969. This figure represents an incidence rate of 318 new cases of cancer for each 100,000 people in the U.S. population. The incidence rate for blacks (338) is substantially higher than for whites (311). The difference is particularly large between black males (371) and white males (335).

In 1973 the Institute began a new program called SEER (Cancer Surveillance, Epidemiology and End Results Reporting). Using data collected by a selected number of population-based cancer registries throughout the country, the Institute obtains information that may help identify causative or prognostic factors in cancer. The data describe trends in the incidence of the various forms of cancer in the U.S., variation in the occurrence of cancer among different population groups and in different geographic areas, and changes in diagnostic and treatment practices and in survival rates.

A broad range of studies funded by other Government agencies and private organizations, as well as a variety of national and international studies, complement the work in epidemiology of the National Cancer Institute. Some of the international studies are described in a following section.

Chemical Carcinogenesis. Discovery of relationships between exposure to environmental chemicals and the development of cancer in man has usually been the first step toward knowledge about most specific cancer causes. This provides the rationale for an extensive research effort to identify cancer-causing, or carcinogenic, chemicals in our environment.

The Institute conducts its research according to five coordinated program approaches: (1) identification and characterization of population groups at risk for different cancers; (2) identification of the cancerous activity of selected agents by bioassays, which determine the active power of a chemical by noting its effects on animals; (3) development and selection of biological models for bioassay, for the characterization of cancerous processes, and for correlation with man; (4) identification or process required for the cancerous action of selected agents as targets for corrective measures in man; and (5) development, application, and evaluation of those corrective measures.

A listing of the agents presently known to produce cancers in man includes some 10 specific chemicals, 12 mixtures and crude products, and in addition, radioactive materials and radiation (including X-rays and ultraviolet light). The number of items is relatively small because the identification of an agent as directly causative of cancer in man requires large-scale and time-consuming epidemiologic studies, which have been conducted for a very small proportion of the agents that may be carcinogenic.

Some 75 to 80 percent of human cancers are believed to have environmental causes. In the effort to identify cancer-causing agents, the Institute currently tests more than 250 chemicals a year to see if they cause cancer in animals. The chemicals tested include air pollutants, industrial chemicals, agricultural chemicals such as pesticides, food additives such as saccharin and other artificial sweeteners, drugs, household chemicals such as detergent additives, and naturally occurring substances such as products of molds and fungi. Each evaluation requires about four years and more than 400 animals. Approximately 6,000 chemicals have been tested so far, and about 1,000 of them have been found to cause cancer in animals. Based on results obtained in such tests, actions by regulatory agencies and by certain industries have been effective in removing some hazardous chemicals from our environment.

The major types of cancer in man that can be directly related to known carcinogenic exposures are: (1) cancer of the lung, related to cigarette smoke and certain other inhalation hazards (particularly asbestos, chromates, and radioactive materials); (2) cancer of the skin, related to exposure to a variety of crude tar products and of radiation; (3) cancer of the bladder, related to exposure to aromatic amines and their derivates; (4) leukemias, related to exposure to radioactive materials; and (5) mesotheliomas, related to asbestos exposure. A number of human cancers are thought to be related to exposure to environmental carcinogens, but the evidence is less clear.

Because of the widespread use of some of these materials, the proportion of the total population exposed and affected is extremely difficult to estimate, with the exception of such materials as cyclamates, DDT and tobacco smoke. It has been estimated that the majority of the present cases of lung cancer in the United States are attributable to cigarette smoking.

The data from these tests are being recorded in a Computerized Bioassay Data System, which the Institute operates in collaboration with the NIH Division of Computer Research and Technology (DCRT). The System will store the vast quantities of information from the screenings and facilitate analysis of results.

The Institute is also working with the International Agency for Research on Cancer, a component of the World Health Organization, to establish an international registry of chemicals undergoing long-term tests. The registry should prevent duplication of experiments and facilitate world-wide exchange of information.

Because almost all materials that have been demonstrated to be cancerous in man have also been found to be cancerous in animals (even though the reverse is not true), new or improved tests for cancerous hazards in animals are being developed. Other research centers on developing screening methods for cancer-causing chemicals using human tissue cultures. Such a system would evaluate human carcinogenic potential of chemicals more directly than animal systems, and do so far more rapidly and at much less cost.

In collaboration with the National Heart and Lung Institute, the Department of Agriculture, and the tobacco industry, an effort is under way to develop less hazardous cigarettes. A special battery of tests is being used to determine the relative hazards in tobacco smoke from a variety of experimental cigarette types.

A key to controlling the action of carcinogens on target cells is in the understanding of how enzymes can impede or block the action of carcinogens. Most progress in this field has been in defining the activation of polycyclic hydrocarbons. These chemicals, generally present in combustion products, polluted air, smoke and industrial wastes, are made carcinogenic by the action of enzymes in body cells. Current studies are measuring enzyme profiles in human populations to determine their relationship to carcinogen susceptibility.

Considerable progress has also been made in the identification and study of a major class of potent carcinogens, the N-nitroso compounds. The mechanism of their formation in the body has been demonstrated, and conditions have been identified under which their biological activity can be inhibited.

Viruses and Cancer. The Institute is responsible for planning and conducting a program of coordinated research on viruses as possible causative agents in human cancer. Scientists not only provide the broad operational management for intramural and collaborative research but also conduct investigations on cancer-causing viruses and their interaction with host cells. Any information obtained from these coordinated studies is rapidly applied (1) to the search for viruses or virus genetic information which may be causally related to human cancer and (2) to the development of therapeutic and preventive measures for control of human cancers when such causative agents are found.

The world of viruses is large and includes entities that are quite different in size and in chemical structure. Viruses are cell parasites that can replicate only within animal or plant cells. Structurally they are either deoxytibonucleic acids (DNA) or ribonucleic acids (RNA), a series of nucleic acid components (purines and pyrimidines) attached along backbones of sugar-phosphoric acid building blocks. The nucleic acids are structurally similar to the hereditary components of all animal and plant cells. During the extracellular phase of virus existence, the nucleic acids are contained in a protein coat, which is shed when the virus enters a cell. The type of cellular reaction produced by a virus apparently depends upon the degree to which the host can resist viral invasion. In the true invasive cancers, the causative virus is difficult to recover.

There are over 120 viruses that cause cancer in animals, and they may be found in both the DNA and RNA categories. RNA viruses cause leukemias and solid tumors in many animals, such as chickens, mice and cats. This category of viruses is therefore an excellent candidate for a possible causal role in human cancers as well. DNA viruses of the herpes type, which are commonly found in man, also have been associated with certain human cancers. In particular these viruses have been linked to cancer of the uterine cervix, nasopharyngeal cancer, Hodgkin's disease, and Burkitt's lymphoma. The Institute supports studies of both categories of viruses to determine whether infection by these agents can, for example, either prime a cell for cancerous change or, in certain circumstances, cause cancer directly. Scientists are also evaluating the possibility that one or more combinations of environmental and host factors may interact with viruses to promote the onset of cancer.

The discovery in 1970 of an enzyme, now called reverse transcriptase, in the RNA cancer viruses of different animal species spurred much of the subsequent research on these viruses. This enzyme enables viral RNA to make DNA copies of itself, a pattern which may help explain the virus' cancer-causing activity. Until 1970 biochemists believed that genetic information could only be copied, with enzyme help, from DNA into RNA or other DNA copies.

The Institute directs much of the research toward development of techniques to detect RNA virus information in human cancer tissues. Three new techniques, developed since 1970, have enormously increased the possibility of finding such viral information: (1) new immulogic methods to detect viral expression--the presence of either the whole virus or any of the tell-tale viral proteins: (2) specific ways to activate viruses in tissues, and (3) techniques to detect viral activity at the molecular level.

The evidence that viruses play a role in human cancer is mounting. Particles that resemble viruses have been seen under the electron microscope in cells from patients with acute leukemia, various other cancers, and rectal polyps. Sophisticated biochemical methods have yielded evidence that human breast cancer and leukemia contain RNA similar to that found in mouse tumor viruses, and that some human acute leukemic cells contain an RNA virus-associated enzyme.

On the other hand, considerable evidence, much of it epidemiologic, suggests an association between a herpes virus known as type 2, a common parasite of the human urogenital tract, and cancer of the uterine cervix. Recent biochemical studies of the DNA core of this virus show a relationship between the viral DNA and hereditary information in infected human cervical cancer cells. Another herpes virus under study is the Epstein-Barr virus, which may be a contributing factor in the causation of Burkitt's lymphoma, and which possibly is associated with other diseases as well.

Such evidence is suggestive but insufficient to establish viral causation of human cancers. Up to now, no human cancer has been demonstrated to be due to a virus, although many scientists think it is only a matter of time until this is achieved.

However, studies of the biochemical events that occur during cancerous infection of cells by viruses provide information on virus expression and regulation that may lead more rapidly to new methods for detecting or controlling human cancer at the cellular level. Viral transformation of a cell involves production of characteristic enzymes and alteration of the cell's surface. Some of these changes may be detected by the appearance of antigens that stimulate the production of antibodies, substances formed by the body's immune system. Techniques for detecting these immune markers may be used to indicate the presence of cancerous cells or to monitor the progress of treatment. New methods of treatment may become possible by blocking or even reversing the enzymatic and surface changes that accompany viral transformation.

In FY 1975 research on cause and prevention will involve: search for NRA viruses that cause cancer in man; exploration of the role of certain DNA viruses as causative agents of lymphomas and carcinomas, either as carcinogens or cocarcinogens; explanded industrial epidemiology research to include studies for possible effects of air pollution on lung and stomach cancer rates in urban areas; efforts to increase and improve assessment of carcinogenic potential of environmental and industrial chemicals; studies in *in vitro* and "host-mediated" bioassay of chemical carcinogens; investigation of smoking habits and efforts to develop a less hazardous smoking product; identification of high-risk populations and investigation of correlated dietary and other factors; special collaborative ethnic studies of identified high-risk groups; expansion of epidemiologic studies of human breast cancer to determine possible viral etiology; genetic aspects of cancer causation; data and analytical support of clinical cancer research centers through the Cancer Surveillance, Epidemiology, and End Results (SEER) reporting program; and stronger and more flexible computer programming, information systems, resources, and systems analysis support of etiologic research in the Institute.

Detection and Diagnosis

Most physicians believe that early diagnosis of cancer offers the best means to reduce the rate of deaths among cancer patients. Small cancers that have not yet spread can be removed surgically with an excellent chance of cure. Even if the surgeon cannot remove all the tumor, the earlier the disease is diagnosed, the better are the results of available radiation and drug treatments. This emphasis on the importance of early diagnosis is likely to be justified for some years to come, despite the increasingly productive research efforts on therapy with drugs and other modes of treatment. Furthermore, evaluation and application of the many exciting research results in chemical and viral carcinogenesis will take still longer to reduce cancer incidence.

Research in cancer detection and diagnosis is being directed increasingly toward early diagnosis of cancers of the major organs at stages when the cancer is still curable by surgery. These cancers, including lung, breast, uterus, large bowel, bladder and prostate, encompass at least 60 percent of all human cancers, excluding cancer of the skin.

Much of the research in cancer detection is directed toward development of techniques for screening large numbers of people. Cancer diagnosis is concerned with providing information for the treatment of cancer. This information may include the location of cancer cells in the body, the type of cancer cells involved, and the ability of the patient to resist both the spread of cancer and the side effects of cancer treatment.

Advances in basic cancer biology and immunology are an important source of progress in the detection and diagnosis program. Breast cancer, for example, may involve several types of cancer cells with different susceptibilities to causes and treatments. Hormones may stimulate the development of some breast cancers but not others. Treatment may be more effective if this hormone dependency can be diagnosed and taken into consideration. A major effort is concerned with identifying cancer antigens are carcinoembryonic antigen, associated with bowel cancer, and alpha-feto-protein, associated with liver and testicular cancers. Although use of these antigens in cancer detection may be limited by their occurrence also in patients with diseases other than cancer, the antigens may prove to be valuable as "markers" to follow the progress of patients under treatment.

Cytologic examination, the study of the characteristics of individual cells, has been used for some 30 years in the Papanicolau smear for the diagnosis of cervical cancer and pre-cancerous conditions. This kind of examination is now being used also on cells in sputum to diagnose lung cancer. Use of the Pap smear has been given major credit for the decreasing death rate from cervical cancer in this country. The death rate could be reduced further by regular testing of all women, but the number of tests to be done would overwhelm the technicians available to do them. To improve the efficiency of cell analysis, the Institute has begun a program of cytology automation. Computer analysis of cells has been attempted in many laboratories. A promising new approach is the development of a device to separate cancerous from normal cells in suspension by their size and light absorption in a laser beam. These machines may be able to identify normal specimens and thus reduce the number of specimens that the technician must study.

Radiologic techniques are very important in the diagnostic location of cancer in individual patients. Among cancers diagnosed in this way are those of the prostate, larynx, rectum, bladder, lung and breast. X-rays of the breast, using a conventional film technique known as mamography or the newer technique of xeroradiography, are most useful in screening examinations for cancer of that organ. Thermography and ultrasound are two other techniques under study in the diagnosis of breast cancer, attempting to detect the presence of tumors by abnormalities in surface temperatures or transmission of sound, respectively.

A major advance in the clinical diagnosis of cancer was the Japanese development of fiberoptic examining instruments for locating tumors by direct observation deep within body passages. These devices include a fiberoptic colonoscope for visualization of the large intestine and a fiberoptic bronchoscope for probing all the major areas of the lung.

The Institute is supporting the development of screening programs for cancers of the breast and lung, the cancers that cause more cancer deaths among women and men, respectively, than any other individual forms of cancer. Methods proven effective in early detection in research at single institutions are demonstrated to the medical community through the

Cancer Control Program. The Institute and the American Cancer Society are cooperating in a joint program of demonstration screening centers for breast cancer. Twenty-seven screening centers are being established throughout the U.S. Each center will provide free examinations to at least 5,000 women annually, including a medical history, palpation, mamography or zeroradiography, and thermography.

Lung cancer screening programs are being supported by the Institute at three centers: The Johns Hopkins University, Baltimore, Maryland; Memorial Hospital for Cancer and Allied Diseases, New York City; and the Mayo Clinic, Rochester, Minnesota. Men who are regular cigarette smokers and thus at high risk of developing lung cancers are examined by chest X-rays and deep cough sputum samples. Any detected cancers are located by a variety of techniques, including flexible fiberoptic bronchoscopy. The bronchoscope can locate lung cancers one-tenth the size of cancers observable in chest X-rays.

Provision will be made in FY 1975 for studies in early detection and diagnosis that have a high probability of early success in reducing cancer mortality. Demographic studies to identify high-risk population groups as part of the SEER program will continue. Work will be expanded in the development of automated procedures and machines for cancer cytology. They will include both flow-through equipment for cell separation and computer-assisted methods of pattern recognition for the identification of abnormal cells. Increased support will be provided in the very promising area of identification of tumor antigens for screening tests and also in the development of tests for hormones produced by certain tumors. Work will start on a more specific test for human blood in the feces; such a test, which now seems possible, would provide a simple method of screening for bowel cancer.

A program will be initiated to improve methods and equipment for X-ray diagnosis of cancer. A truly effective method will be sought for bowel cleaning before a barium enema to diagnose bowel cancer, to save the vast amounts of patient and doctor time lost in repeating the procedure. In X-ray equipment, computer enhancement and plotting of images will be investigated, as well as the use of computer analysis of X-rays done in volume, such as those of the chest. In both diagnosis and in prognosis, increased emphasis will be placed on the broad application of new and existing methods through the Cancer Centers Program.

Reduction in mortality from cancer of the lung now appears possible through early detection by regular cytologic examination of the sputum. In a long-term study of sympton-free middle-aged male cigarette smokers, cells suspicious of cancer have been found in nearly 1 percent of those tested in a period of a year. This same study of men at high risk of lung cancer has provided a major diagnostic advance. Finding suspicious cancerous cells in the sputum cannot indicate the location of the disease in the lung, nor are small surgically curable cancers visable on X-ray however, with the flexible fiberoptic bronchoscope, it has been possible to find almost every such cancer and pinpoint it to guide the surgeon. This work will be expanded.

There will be expansion of clinical testing of the ability of assays of estrophile proteins in breast cancers to select patients who will benefit from hormone ablative surgery. Plans will be developed for large-scale clinical trials to improve tumor pathologic staging and correlate it with the clinical course of the disease.

Treatment

The long-term objective of cancer treatment is to cure or control cancer in man. Immediate objectives are to increase the number of patients responding to therapy and to prolong the period of disease-free remission and survival.

Surgery continues to be the most widely used form of cancer therapy. Surgical procedures have been made more successful in recent years through better understanding of the physiology of cancer patients, better devices for patient monitoring, and use of new antibiotics to control infection.

Surgery is the primary treatment used for lung cancer, the form of cancer that claims the most lives in the United States. Cancers of the breast, intestine, rectum, uterus, and stomach are also treated most effectively by surgery. In general, survival rates after these operations have been improved by advances in early detection of these cancers.

A major study, headquartered at the University of Pittsburgh, is under way to decide the vexing problem of how extensive surgery must be to get the best possible results in breast cancer. In the United States, the most widely used operation for this type of cancer is known as a mastectomy, in which the affected breast is removed. Removal of some apparently healthy tissue surrounding the breast is generally recommended, although the extent of surgical excision in early breast cancer is the subject of some professional controversy. The study will also evaluate other procedures for breast cancer treatment, including radiation and drug therapy.

Studies by Institute investigators include surgical treatment of difficult cancers such as melanomas, certain solid tumors, cancers of the head and neck, and advanced and recurrent cancer of the cervix. Except for solid tumors of the bone, results have been encouraging, with five-year survivals of 40 to 50 percent.

Radiotherapy for cancer treatment has become increasingly important in the United States during the past two decades. Currently, it is used either for control or for palliation in an estimated 50 to 60 percent of all cancer patients at some stages of their diseases. To be effective, a radiation dose must be large enough to destroy cancer cells, but not so great as to seriously harm normal tissue surrounding or overlying the cancer. Radiotherapy is particularly effective in treating small, localized cancers made up of radio-sensitive cells and located in sites inaccessible to surgery. Sometimes radiation is delivered to apparently normal tissue as means of preventing later recurrence of the disease due to undetectable spread.

Institute physicians have demonstrated the value of radiation in the treatment of early Hodgkin's disease, with increases in five-year survivals from 60 percent to 90 percent. Similar radiation treatments, to include probable but inapparent areas of cancer spread, have also been useful in lymphosarcoma. An aggressive program of radiation and drug treatment is increasing survival rates in patients with Ewing's sarcoma. A similar program of combined therapy is now in progress with patients with lung cancer.

The intensive use of combinations of drugs or drugs plus surgery and radiation has changed the whole outlook of patients with some presumably fatal cancers. Within recent years the increased use of multiple anti-cancer chemicals has brought about substantial rates of remission and long-term, tumor-free survival in acute lymphocytic leukemia and Hodgkin's disease, and remissions in a number of other fast-growing tumors such as lymphomas and certain soft-tissue sarcomas.

The Institute has led the national effort to achieve chemical control of cancer since a program in this area began in 1954. This systematic attack was undertaken on the part of the Government to fill a need that was not being met by either universities or industry because of its extremely high cost. The effort encompasses every phase of drug development, beginning with the acquisition of natural products and the synthesis of new compounds through the completion of clinical trials and the introduction of active anti-cancer drugs into medical practice.

To identify active drugs on the basis of observation, scientists use a "screen" of animal tumors and tissue culture systems to predict a substance's activity against human cancer. A total of 30,800 new compounds were tested by the Institute in calendar year 1972 as potential anti-cancer agents. These include approximately 16,000 synthetic chemicals, and 14,800 natural products from fermentation, plant, and animal sources. From 1971 to 1972, there was a 79 percent increase in the number of tests of the materials against various animal tumors and cell systems.

The broader search for new anti-cancer drugs requires a larger input of chemicals for screening and the use of more animals. In order to keep the cost at a reasonable level, the Institute has developed a "mini-screen" which will make it possible to increase in cost. Field tests of the mini-screen are now complete, and the system will replace the older more extensive screen.

From the operation of this program over the last 15 years, there has come a sound body of data on the chemical control of clinical cancer and a precise knowledge of the confidence that can be placed in the animal systems in predicting what will happen in man, both with respect to effects upon the tumor and effects upon the patients. There are now about 40 drugs that have been shown to cause regression of some type of clinical cancer.

However, the tumors that are highly susceptible to drugs constitute only about 15 percent of clinical cancers. Only two cancers, choriocarcinoma and Burkitt's lymphoma, can be cured by the use of a single drug. Remissions are being achieved through the use of drugs in patients with adenocarcinoma of the ovary, multiple myeloma, non-Hodgkin's lymphomas, and adenocarcinoma of the breast. The prognosis for survival of these patients has been improved, although it is too early to speak of cures. In all instances, either a combination of drugs is required or drugs must be used in combination with surgery and radiation to kill those tumor cells that have been left behind by these two treatments. In a limited number of cancers, such as acute lymphocytic leukemia, Hodgkin's disease, rhabdomyosarcoma, testicular tumors, Wilms' tumor, Weing's tumor, and retinoblastoma, combinations of drugs or drugs combined with another type of treatment can result in a normal life expectancy in significant numbers of patients.

Among new anti-cancer drugs, Adriamycin, discovered by Italian scientists, is the most important new agent under investigation. It has been tested in 1,000 patients with a wide variety of cancers. Significant activity (25-50 percent response rates) has been demonstrated against sarcomas, lymphomas, leukemia, neuroblastoma, breast cancer and lung cancer. There was also preliminary evidence of significant activity against bladder cancer, Wilms' tumor, multiple myeloma, and testicular cancers. Side effects included cardiac toxicity, and this was not always predictable and manageable. Investigations are under way to discover chemicals analogous to Adriamycin which retain the anti-cancer activity of the drug but cause no cardiovascular damage.

A key element in the successes in treatment has been the Institute's development of a team of scientists and physicians with the expertise and resources to do fundamental research and, at the same time, to initiate and manage all steps required for optimal application of this research knowledge for the benefit of cancer patients. To do this job, the Institute obtains the advice of outstanding individuals from outside the Institute, both in the United States and abroad.

The various steps leading to chemical control of cancer have been set down in a logical sequence. This "linear array" (overall plan) delineates the steps necessary to move from the acquisition of new agents to definitive clinical trials in man, with decision points at regular intervals where it is decided whether to continue or not. Similar plans are being made to develop and evaluate new combination treatments, using drugs, radiation, surgery and immunotherapy, with the last used at least as a monitor of the effectiveness of the other treatments.

The final steps in this process are clinical trials of new treatments which are carried out in cooperation with many participating institutions. Twenty-one grant-supported cooperative cancer research groups (active and developing) made up of 1,600 investigators from more than 300 different institutions have entered more than 19,000 patients into controlled clinical studies. These cooperative group members annually supervise the treatment of some 95,000 cancer patients and provide consultation regarding treatment for an additional 50,000 patients. Cooperative groups rely upon the Institute's drug development program for both drugs and data required for their clinical research.

The Institute also carried out a world-wide surveillance for leads on new drugs as well as other forms of therapy. Not only are ideas and drugs exchanged, but laboratory and clinical information from other research centers around the world is assembled, analyzed and distributed.

The Institute further serves a national clearinghouse and operations center for much of the work in cancer treatment that is going on in this country. Information on chemical control of cancer, radiotherapy and surgery is collected, analyzed and distributed to interested physicians and investigators. Drugs and radioactively labeled materials, as well as other assistance, are provided to the national cooperative clinical groups and to scientists in laboratories.

Because many initial leads on active drugs in cancer come from empirical observations, an important contribution of the Institute is the investigation of these leads with all the tools provided by modern science, both in its own laboratories and in other research facilities. In this way, these empirical observations can be generalized into sound theory that then becomes a much more precise tool in predicting drug effects in man from animal and laboratory observation.

For the last five years the Institute has been exploiting the drugs active against "old" tumors--that is, tumors discovered late in their natural history. Old tumors generally are less sensitive to drug treatment than "young tumors." Since successful control or cure of cancer thus far has been achieved only in the rapidly growing tumors, there is a broad effort to understand--biologically, clinically and at the biochemical level--the reasons for lack of drug susceptibility of slowly growing tumors. Animal screens that simulate the biology of slowly growing tumors are being sought. Recent experience, however, has shown that the biology of these tumors is complex, and a good deal of additional work will be needed before an appropriate model can be introduced into the program. In addition, biochemical and cell culture screens are being investigated to take advantage of recent developments in understanding the molecular events associated with cancerous change.

Another serious obstacle to the cure of cancer is the inability of the physician to know whether treatment has rid the body of all tumor cells. Clinically diagnosable cancer is associated with a body "burden" of approximately one trillion tumor cells. When treatment reduces the number to one billion cells, the tumor is no longer detectable by present techniques, but it will always return. Consequently, treatment may not be administered long enough or may lack sufficient intensity to bring about cure. Combination drug treatments or combinations of drugs with surgery and radiation may well improve the patient's chances for survival. In order to assess rapidly the curative capacity of combination therapy, a method of estimating the number of tumor cells in the body after each course of treatment is essential and is under development.

Morbidity and mortality from infection, resulting from the side effects of treatment, are another problem. Successes in the prevention and treatment of infections by means of protected environments and white cell transfusions make it imperative to expand clinical use of these techniques. A recent study indicates that deaths from infection are reduced by 75 percent through the use of the laminar flow room, as compared to patients treated on a conventional ward.

In another approach to improved treatment, Institute scientists are investigating ways to monitor the immune status of the cancer patient. Determining how well the immune system of a patient is functioning may guide the physician in scheduling treatments that interfere with the immune system. Finding ways to bolster the patient's immunological defenses against cancer may provide additional hope of prolonged survival.

The FY 1975 treatment efforts will be concentrated particularly on the application of available knowledge and experience to the management of patients with the slowly growing, more common tumors that account for 70-80 percent of all cancer deaths. They include brain tumors, lymphomas, and cancers of the cervix, ovary, breast, bladder, prostate, testis, pancreas, colon, and head and neck. All modalities of therapy will be pursued to strive for maximum effectiveness. However, since combinations of modalities have proven superior to agents used alone in disseminated disease, greater emphasis will be placed on research in both animal tumor systems and in patients in order to identify optimal combinations.

Programs in laboratory and clinical research on the use of BCG and other enhancers of the immune mechanism are under way. It is planned that large-scale programs to evaluate the usefulness of these materials in several different human tumors will be undertaken in the coming year. There will be expansion, too, of current studies of high LET radiation therapy.

Rehabilitation

Prior to the National Cancer Act of 1971, no national program existed for rehabilitation of the cancer patient. Some state and voluntary agencies do provide excellent rehabilitation services to limited numbers of cancer patients. However, only a few institutions in the country are capable of providing comprehensive rehabilitation service to the growing number of patients who are long-term survivors from cancer.

Rehabilitation programs of the Institute are concentrated mainly in the Cancer Control Program and in the program of comprehensive cancer centers. In the Cancer Control Program, rehabilitation projects are essentially independent from other areas of cancer research. Projects deal with all facets of the rehabilitation of the cancer patient, from the palliative and restorative aspects to problems of a vocational or psychological nature. In keeping with the new concept of the "comprehensive center," the Institute's center program supports efforts in developing and providing rehabilitative services for cancer patients within the framework of multidisciplinary centers staffed by personnel involved in every aspect of the cancer problem.

During the past year, a comprehensive planning effort was initiated to develop a national rehabilitation program specifically for cancer patients. More than 100 rehabilitation experts, social service professionals, and former cancer patients cooperated with the Institute in defining specific research and demonstration projects. In the program that has emerged, efforts will be directed toward changing pessimistic and fatalistic attitudes on the part of the medical profession and the public toward the cancer patient. Rehabilitation facilities, techniques, and education programs for a wide range of rehabilitation professionals will be developed to serve the needs of cancer patients. Studies will be supported to find ways of providing rehabilitation services in remote areas of the country as well as in major cancer centers. In addition to seeking ways to improve utilization of existing rehabilitation resources, the national program will endeavor to establish rehabilitation facilities in clinical cancer centers.

To launch the national rehabilitation program, a data base will be required which will include such fundamental information as analyses of facilities, techniques, and professional education programs which now exist to serve patients other than cancer patients. Essential to the program for cancer patients will be an evaluation of the role of psychological and social factors in the tolerance of the patient's cancer diagnosis by the patient himself, as well as by his family, employer and the community.

Support Programs

Research Supported by Grants

The National Cancer Institute supports research activities in all areas of the National Cancer Program through research grants. Grant programs range from projects with single objectives to those that are broadly based and cover multidisciplinary areas. Program directors in the NCI define program objectives, identify areas needing additional exploration, monitor ongoing grants, and coordinate program activities with priorities of the National Cancer Program Plan and with research conducted by NCI staff scientists.

Organ Site Task Forces

Research programs directed toward cancers of major body organs complement the broad research efforts focused on diagnosis, treatment and other disciplines. The task force concept meshes the talents of scientists and clinicians from all cancer research disciplines. Knowledge exchanged through these integrated programs increases comprehension of the causes of specific cancers and of methods to prevent, detect, diagnose and treat them.

Five major forms of cancer are currently under intensive study through the organ site mechanism. These cancers of the breast, lung large bowel, bladder and prostate, account for about 43 percent of new cancer cases expected in 1974 and about 54 percent of estimated 1974 cancer deaths. The Breast Cancer and Lung Cancer Task Forces are funded through contracts, whereas the programs of the Large Bowel, Bladder, and Prostate are supported primarily by grants.

In addition to a task force of medical scientists from throughout the United States, each organ site program is administered by a staff responsible for coordination, evaluation and communication. To broaden the management base for the National Cancer Program, administration of the Large Bowel Task Force is located at the M. D. Anderson Hospital and Tumor Institute, Houston, Texas. The Bladder Task Force is at St. Vincent Hospital, Worcester, Massachusetts, and the Prostate Task Force is at Roswell Park Memorial Institute, Buffalo, New York.

Cancer Centers

Cancer exhibits varied characteristics depending upon its kind, site, causes, state and the personal characteristics of its victims. To combat the complexity of this disease, scientists and clinicians must work together to close the gap between research and treatment.

In 1961 the National Cancer Institute began financial support to institutions that promote a concept of multidisciplinary cooperation and research. These cancer centers provide resources necessary to develop a broad program attracting the interest and participation of scientists and physicians of diverse fields. The overall goal of establishing a network of these centers is to develop and demonstrate the best methods of cancer prevention, diagnosis, treatment and rehabilitation. To meet this goal, the centers provide the most up-to-date patient-care facilities for clinical research and teaching.

Two different types of centers have evolved since the program's inception. Comprehensive Cancer Centers have the capability for the whole range of cancer biomedical research, clinical services, and professional training and education. Specialized Centers, on the other hand, exhibit particular expertise in a limited number of selected activities such as radiotherapy or chemotherapy.

In designating these Comprehensive Centers, the Institute also hopes to achieve an even geographical distribution to ensure that maximum benefits from the National Cancer Program reach the largest possible fraction of the Nation's population.

Currently, 51 existing centers fall in the "specialized" category. Most of these do, in fact, concentrate their efforts on discrete areas of research and clinical activity. However, the responsibilities of some specialized centers have broadened. As a result, such centers may some day be considered Comprehensive Cancer Centers.

Cancer Control

The Cancer Control Program was authorized by the National Cancer Act of 1971 to speed the application of research results for the benefit of cancer patients and those at risk to cancer. Most activities are aimed at controlling the occurrence and impact of the major causes of cancer deaths in this country. The program will include education of health professionals and the public, demonstrations of effective cancer prevention, detection and treatment practices, development of model systems for the treatment and management of cancer patients, and research on more effective means to utilize present knowledge about cancer.

The Cancer Control Program is a coordinated national effort, involving all appropriate elements of the Department of Health, Education, and Welfare, including appropriate components of the National Institutes of Health; other Federal agencies; state and local health departments, and all related organizations and activities of the private health community.

The program has developed rapidly in the relatively short time since the cancer control mandate became effective. For the prevention of lung cancer, the National Clearinghouse for Smoking and Health is being supported in its education programs to reduce the number of Americans who smoke, especially the number of young Americans who acquire the habit. Demonstration screening programs for lung cancer are under way at the Johns Hopkins University, Baltimore, Maryland, and the Memorial Hospital for Cancer and Allied Diseases, New York City. Staff of the West Texas Chest Hospital at Tyler are screening for lung cancer and other asbestos-related diseases among nearly 900 former asbestos workers.

NCI and the American Cancer Society are jointly funding 27 demonstration projects for breast cancer screening by a physical examination, mammography and thermography. Eleven regional networks of community hospitals and physicians are being established to demonstrate breast cancer diagnosis, treatment and rehabilitation. Other regional networks are being established to demonstrate effective diagnosis and treatment practices for acute leukemia, lymphomas, and cancers of the head and neck.

In cooperation with 21 state health departments, the Cancer Control Program is supporting a screening program for cancer of the uterine cervix. Annual Pap tests will be provided free of charge to low-income women in 13 states with existing screening programs. Eight other states with no cervical cancer screening programs will begin planning for such programs.

International Activities

Cancer knows no national or ethnic boundaries. It strikes the strong and the weak in all countries. Thus, the national program to conquer cancer is a commitment of an effort reaching beyond the boundaries of the United States.

An important new program of cooperation between the United States and the Soviet Union began as a result of the President's summit meeting in Moscow early in 1972. A U.S.-U.S.S.R. health agreement was signed, calling for the sharing of results from cancer, heart disease and environmental studies. The Institute has followed through on this diplomatic initiative, and cooperative arrangements have been established in four research areas--cancer chemotherapy, virology, immunology and cytogenetics.

The arrangements provide for:

- Exchange of specialists, including (1) short-term visits of senior scientific investigators of corresponding institutes for the development of concrete plans for cooperative research and for familiarization with results of ongoing research, and (2) long-term visits by young specialists for detailed study of particular problems.

- Exchange of anti-cancer agents for preclinical and clinical study, and of materials such as viruses, reagents, and biological specimens for basic research.

- Joint meetings, publications, and exchange of information in four subject areas.

Scientists from both countries have already visited their counterparts. A number of new anti-cancer drugs have been exchanged, together with all relevant clinical data. The Institute has delivered to the Soviets 31 strains of viruses associated with animal and, perhaps, human cancers. In return, the Institute has received a number of cancer viruses, some of which are believed by Soviet scientists to be human cancer viruses. In addition, information on investigations of postoperative cancer chemotherapy of cancer of the gastrointestinal tract, breast and other sites has been exchanged. Also, agreements in the areas of epidemiology, cancer centers, and cancer control are being explored.

An important effect of this new scientific and technical cooperative arrangement between the United States and the Soviet Union is the strengthening of many other international activities under way in the field of cancer. Operations have been instituted in Belgium and Japan which will increase the screening programs for new anti-cancer compounds and foster the development of new and uniform screening approaches.

Both the International Union Against Cancer (UICC), with headquarters in Geneva, Switzerland, and the International Agency for Research on Cancer, with new facilities in Lyons, France, are receiving considerable financial support from the Institute for research studies. In collaboration with the UICC and the World Health Organization, the Institute recently held a conference on childhood cancer. Major recommendations from that conference will be implemented by some 80 countries throughout the world and are expected to have considerable impact on the source of childhood cancer research. The Institute and UICC are also conducting an international comparison of childhood cancers according to cell type. A working relationship has been developed with the Manchester Childhood Tumor Registry, the only population-based registry concerned with pediatric cancer.

Institute-supported researchers continue to collect valuable demographic information from special populations such as those in India and Cali, Colombia, where there are high incidences of certain cancer types. The Institute supports work aimed at bringing the Cancer Registry of Israel up to a high functioning level, and also continues to tap the migrant Norwegian and Polish population for cancer-related data.

Esophageal cancer has been increasing rapidly in the United States, especially among black males. Epidemiologic studies have been undertaken in collaboration with the International Agency for Research on Cancer to determine possible environmental causes for the extremely high occurrence of this cancer along the southern shore of the Caspian Sea in Iran. IARC is also carrying out worldwide research on Burkitt's lymphoma, nasopharyngeal cancer and lung cancer.

The Institute has provided Hammersmith Hospital in London with trained radiation therapists to assist in the world's first controlled clinical trial of high-energy neutron radiation in the treatment of cancer. This Institute activity not only provides valuable assistance to the London workers but also develops a cadre of United States radiation therapists trained in this sophisticated, experimental cancer treatment technique.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Introduction

The focus of the National Institute of Child Health and Human Development (NICHD) is on growth and maturation, both biological and behavioral, including associated diseases and disabilities, from conception through the early adult years. The Institute is concerned with the human as a developing organism, recognizing that developmental changes are affected by many factors--biological, psychological, social, and ecological. In working toward such important goals as pregnancy without complications, birth without injury, childhood without physical or psychic trauma, and youthful maturation without physical or emotional disability, the Institute draws on the expertise of biological and social scientists throughout the United States and the world.

The Institute has two major divisions, one concerned with population research and one concerned with child health research. Responsibility for research pertaining to maternal health is shared by these administrative divisions, with the greatest effort being supported by the child health conglomerate.

Population Research

Population research encompasses four large and complex undertakings: (1) the development of improved methods of fertility regulation, including the improvement of contraceptive technology and control of infertility; (2) studies of biologic and genetic implications of contraceptive use; (3) investigations of the social and behavioral aspects of population problems and dynamics; and (4) basic biomedical research in the population sciences.

The NICHD is the focal point for population research within the Federal Government, committed to study not only the biological and medical aspects of reproduction and fertility, but also the psychological, socioeconomic and cultural factors with which they are intertwined.

Individual and mass fertility have profound personal and social consequences throughout the world. Recognizing this truth and the impact of birth rate and population size on the overall quality of life, the Federal Government in 1972 instituted a Five-Year Plan for Family Planning Services and Population Research. This plan supports research in the population sciences, provides the opportunity to inform all persons of the consequences of their individual reproductive acts, and assists them in family planning that is efficient and compatible with their own ethical values.

Such developments will enable couples to have children only when they want them, to space them so that each child may achieve optimal development, and if desired, to avoid childbearing in the early and late reproductive years when the risks of bearing premature and mentally retarded children are the greatest. The Institute's behavioral research is expected to yield an understanding of reproductive motivations and to reveal how economic development and population size, growth and distribution are interrelated.

While much progress has been made in the development and acceptance of contraceptive drugs and devices, contraceptive methods to suit the needs of every individual seeking control of fertility have not yet been developed. The NICHD, therefore, continues research to develop new methods of contraception and to evalute current techniques. To complement this program the Institute is supporting the synthesis and testing of new drugs which may prove to be acceptable to various segments of the population. In addition, the Institute is supporting the development of reversible sterilization techniques for both men and women.

Despite the widespread use of oral contraceptives, they are relatively new and their long-term effects are not well known. The Institute seeks more knowledge of their medical effects, including their relation to cancer of the cervix and breast, to nutritional biochemistry, to increased incidence of clotting and blockage of blood vessels, and to other disease states. The effects of steroid contraceptives and intrauterine devices on future generations, especially their possible relation to birth defects, are of interest. Studies of animal models to permit better prediction of adverse effects are also being supported.

Basic knowledge of reproductive processes in humans and animals has the immediate goal of promoting the development of new contraceptive methods and is important in understanding fertility and sterility. As the major supporter of fundamental research in reproduction, the NICHD is providing the basis for the solution of new problems related to the reproductive process as they are perceived through time.

The ultimate goals of population research in the social sciences are to ascertain the extent and nature of population problems in this area and to suggest possible solutions. These problems are being examined from several points of view--including those of the individual and of the limited and extended social groups to which the individual belongs.

A major task of this line of population research is to understand why couples might choose one family size over another and to analyze consequences which might evolve from these decisions. It is also necessary to know more about factors operating in remarriage, urban migration, the availability of effective and acceptable contraceptives, and attitudes about ideal family size. The economic cost of children, social mobility and aspirations, and the desire to follow certain life styles also affect fertility decisions. Moreover, the role of the male in making decisions regarding fertility and its regulation needs to be explored further.

The relationship of population growth to demand on available resources, including living space, in various and social and geographic settings will receive increasing attention among social scientists involved in population research.

Child Health

The Institute's responsibility for research pertaining to child health begins with implantation of the embryo in the uterine wall and extends through adolescence into early adulthood. Inclusion of early adulthood permits the conduct of longitudinal studies to determine the effects of early intervention on the maturation process.

Research efforts focus on the health of the mother; the effect of her health on the child both before and after birth; and the well-being of the fetus, the birth process, and the adjustments of the infant to the extrauterine environment. The focus then shifts to the study of nutritional, hormonal, social, psychological and other factors relating to the kind of adult the individual will become. Investigations are concerned with normal and aberrant development.

The NICHD effort promotes coordinated research to enhance knowledge of maternal health, pregnancy, embryonic development, fetal growth, and infant well-being through the first year of life. Research activities are also directed toward ameliorating infant morbidity, preventing infant death, and narrowing the gap between the identification of new knowledge and its incorporation into the delivery of health care. The Institute supports fundamental research projects in molecular and cellular biology. These include, among others, studies on the development of the endocrine and immune system, the organization of cells, and morphogenesis.

The general health of the pregnant woman, her acute and chronic illnesses, the drugs she takes, the foods she eats, environmental influences, emotional stresses, and social factors have profound effects on the developing fetus. Any of these factors or a combination of factors could be responsible for loss of the fetus or for death of the infant shortly after birth.

The NICHD supports research directed toward the identification, prevention and control of these problems during pregnancy, and aims to identify other health problems of the mother that hold particularly high risks for her and her fetus. Birth defects are an important area of research supported by the Institute. Approximately 3.5 percent of all newborn babies in this country show evidence of a congenital anomaly during the neonatal period, and by the end of the first year, as many as 7 percent of all infants have identifiable defects. Some of these appear to be due to genetics alone, others to environmental factors, and still others to a combination of causes where genetics and the environment may have significant influence.

The highest incidence of infant mortality occurs during the first four weeks of life. Some of the Institute's research aims to increase existing knowledge about the processes of later fetal development, birth, and immediate postnatal adjustment to life outside the uterus. Such knowledge should contribute to a reduction in the number of prematurely born babies and babies of low birth weight who account for nearly 70 percent of deaths during the neonatal period. About three of every thousand infants born alive are victims of the sudden infant death syndrome (SIDS). Suggested causes for the syndrome include infection, cardiopulmonary failure, and aberrant neurophysiologic patterns of response during sleep. It appears that the syndrome is closely associated with maturational and environmental threshold phenomena. The Institute will continue its pursuit of knowledge which will contribute to prevention of this syndrome.

The child who completes the first year of life, essentially intact, has successfully run the gauntlet of infancy and is presumed to be prepared to accept the challenges of childhood and adolescence. A myriad of factors then determines what sort of person that child will become. Through its programs, the Institute sponsors wide-ranging research to learn how both biological and behavioral intervention in a child's life affects normal and abnormal growth and development. For example, the impact of a number of developmental factors on immune development early in life may also program response to disease in later life; poor nutrition may have a number of subtle effects on the individual, in addition to obvious growth failure; since learning begins within the first week of life, it is important to know what stimuli may be helpful or harmful to the developing infant and child.

It is estimated that of the 116 million babies born in the world each year, up to half are undernourished during their first three years of life. In both animals and man, malnutrition has been found to have its greatest effects on mental capability during the most rapid period of brain growth and development--from the last three months of pregnancy up to about three years of age. Although it has been clearly established that severe malnutrition during the first two years of life can lead to shorter stature and lighter weight, effects of undernutrition in early life on biological and behavioral development have not yet been determined. Uncertain availability of sufficient food to satisfy hunger may have important effects on cognitive development, susceptibility to certain diseases, development of digestive function, and the evolution of productive social behavior. The Institute will continue to be interested in research pertaining to these nutrition-related problems.

A number of studies currently supported by NICHD involve learning and early cognitive development (thinking): that is, how a child processes, abstracts, and generalizes information into strategies for problem solving. Research is aimed, particularly, at determining how the learning process can be improved in children where learning is impaired because of biological, behavioral, and/or environment deficits. There is also interest in supporting research which will elucidate how children acquire language and how they develop the capabilities that will be used as adults in communicating via spoken language and in reading written language.

The Institute supports anthropometic studies of growth in various populations under varying environmental conditions; ultrastructural studies concerned with changes in body composition during growth and development; and longitudinal studies to determine individual patterns in physical growth over time.

The Institute focuses much attention on the role of hormones in growth and development and on how the endocrine system itself matures through time. Such studies may pinpoint critical periods when hormonal action or intervention programs might be used to treat such problems as dwarfism, giantism, precocious sexual development, and retarded physical maturation. Further research is needed to learn how environmental stimuli, including stress and deprivation, may affect hormone responses later in life. Early environmental effects, along with genetic influences, on the developing central nervous system are also of research interest to the Institute. Several studies are being supported to learn how the body's complex defense mechanisms are organized and how they change with biological maturation. These include basic studies of cellular immunity and studies of how environmental and nutritional factors influence the overall ability of the individual to combat infection and disease. To learn more about the way in which the developing child handles pharmacologic agents, ontogenetic research is being supported in order to better understand age and hormonal influences on the metabolism of drugs. In investigation of four common childhood diseases, absorption, distribution, metabolism and excretion of drugs are being measured.

Institute emphasis during the growth and development years is not only on the very young child, but on the adolescent. A major research effort concerns the mechanisms whereby hormones and enzyme function exert their influence. Of particular interest is the onset of puberty, including the biological mechanisms that underlie this rapid period of growth, and the profound physiological and psychological events that surround it.

The Institute's interests in research on adolescence include: the qualitative change in intellectual development which takes place during adolescence and the important interaction of cognitive processes with motives and attitudes; adolescent socialization, particularly how social patterns affect role behavior; the relationship between physiological changes during adolescence and psychosocial development; and the impact of undernutrition and its sequellae on the biological and behavioral maturation of the adolescent and young adult.

The Institute's research effort in mental retardation is directed toward developing new techniques and perfecting current procedures to detect early conditions associated with developmental disabilities that are associated with damage to the central nervous system. Finding the causes of mental retardation is a primary goal of the NICHD, for pinpointing causes will speed the development of ways to prevent the problem. Where prevention is not possible, identifying, through research, methods of reducing human suffering and ameliorating the consequences of mental retardation becomes a primary goal.

The biological causes of mental retardation are many and varied: it may result from hereditary causes such as inborn errors of metabolism (for example, phenylketonuria, or PKU): from chromosome abnormalities (such as Down's syndrome, or mongolism); from endocrine dysfunction (such as cretinism); from intoxication (such as lead poisoning); from poor perinatal care; and/or from viral infections of the mother which affect the infant at critical stages of embryologic development (such as rubella). Functional mental retardation may result from the trauma of impoverishment, societal denigration, and family crisis.

Support of research aimed at preventing both biologically determined and functional mental retardation will continue to be an important effort of the Institute.

NATIONAL INSTITUTE OF DENTAL RESEARCH

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NATIONAL INSTITUTE OF DENTAL RESEARCH

Introduction

Oral-facial diseases and disorders encompass a spectrum of health problems of differing magnitude and severity. They range from the ubiquitous infection of tooth decay to such dread but less prevalent afflictions as cancer. Although the most common oral diseases do not endanger life, their total impact on the physical, mental, and social well-being of millions of Americans is immeasurable. Very few people escape one or another of these disorders at some time during their lives.

As health expectations of Americans rise, and as preoccupation with the major killers and cripplers shifts to encompass all conditions that harm the quality of life, oral diseases are assuming a more prominent position in the health arena.

Diseases and disorders of the mouth are unique problems. They are largely irreversible, for the body lacks the inherent power to repair most of the damage they inflict. Despite continuous improvements in treatment and control, the major problems of caries (tooth decay) and periodontal (gum) diseases cannot be adequately overcome with corrective measures. Thus, unlike medicine's brilliant successes with cures, dentistry must stress prevention.

Further, the mouth is a complex system of organs and tissues that affects not only our general health but behavior and personality as well. Conversely, the mouth mirrors the health of the total system. Of vital medical importance, the mouth also serves as the most accessible site for the study of basic life processes and of various factors that affect many organ systems and parts of the body.

Today, only a small fraction of the people in the United States get reasonably complete dental care. Almost half receive no care at all. If demand were to parallel need more closely, it would overwhelm professional and auxiliary manpower, despite any realistic increases in their numbers. The solution must ultimately depend on research to devise simpler, more effective means of control, treatment, and ultimately prevention.

Toward this end, a broad program of research, encompassing laboratory, clinical and epidemiologic studies and field trials, is carried out by the National Institute of Dental Research through intramural, extramural, and collaborative (contract-supported) projects. To assure an adequate pool of dental scientists to meet the pressing research needs in this field, training and fellowship programs are also supported.

NIDR activities can be discussed under the following headings: caries, periodontal and soft tissue diseases, restorative materials, craniofacial anomalies, dental research institutes (centers), and training.

Caries

Dental caries is localized, progressive decay of the teeth, initiated by demineralization of the outer surface of the tooth due to acids produced locally by bacteria that ferment dietary carbohydrates. As tooth mineral is lost and tooth protein destroyed by continued bacterial action, cavities form. If untreated, they extend and destroy most of the tooth, often leading to serious infection of the surrounding tissues.

In addition to its sequalae of pain, infection, and tooth loss, caries has a substantial economic impact. Although only a fraction of the need is met, over two billion dollars are spent annually to restore carious teeth. The cost of restoring all cavities which occur each year is estimated to be over ten billion dollars. Even at the existing level of restorative care, it is estimated that 107 million educational and labor hours are lost to undergoing dental treatment.

Dental caries affects 98 percent of the U. S. population. It is probably one of the most common causes of pain and debilitation in children. By the time he reaches school age, the average child has three decayed teeth, while the average 15-year-old has eleven decayed, missing, or filled teeth.

A representative picture of the problem in young adulthood is provided by recent data from the U. S. Army showing that every 100 inductees require 600 fillings, 112 extractions, 40 bridges, 21 individual crowns, 18 partial dentures, and one full denture.

Through its National Caries Program, implemented late in FY 1971 as a Presidential special initiative, the Dental Institute attempts to reduce the incidence of caries and to extend the capability of the dentist, the hygienist, and others on the dental team to prevent decay. Because of the complex nature of caries, it is unlikely that any one approach will completely solve the problem of its prevention and control. Efforts are therefore directed to depressing the effects of all factors to a minimum through a combination of techniques.

Program strategy thus focuses on the development of agents that inactivate the microbial process of caries, that increase the resistance of the tooth to caries, or that decrease the potential of the diet to support caries. The challenging and complex problem of the delivery of preventive methods to the public will also receive increasing attention.

In studies directed at protecting the teeth, outstanding protection against caries has been demonstrated by an adhesive plastic which seals the pits and fissures of the chewing surfaces of the teeth. Current studies involving larger groups are intended to assess the retentive and caries-protective properties of the sealant for up to four years and to evaluate the time and skill required for its application on a mass basis.

Alternative means of providing fluoride are also being studied to bring its benefits to communities that do not or cannot utilize water fluoridation and to achieve further caries reductions. (Fluoridation of public water supplies achieves a reduction in caries incidence of up to 60 percent.) Particularly promising among the new fluoride agents being tested are the amine fluorides. In addition to strengthening the enamel with fluoride, they are believed to inhibit bacterial metabolism, thus providing double-barreled protection against caries. Combinations of fluoride regimens, such as fluoride tablets, mouthrinses, and dentifrices, are also being tested for increased caries prevention, as also is the combined use of a sealant and a fluoride gel.

New findings from animal studies suggest that, under similar conditions of dietary challenge and bacterial composition, constant low levels of fluoride in the mouth may provide more protection against caries than the accumulation of a high level of fluoride incorporated in the tooth enamel. If further borne out, these findings may well change present concepts of topical fluoride therapy.

In the present state of knowledge, the restriction of sweets, particularly those taken as between-meal "snacks," is a necessary part of the regimen for avoiding caries. However, because of cultural influences, it is difficult to motivate people to change long-entrenched habits. For this reason, alternative sweeteners to cariogenic sucrose, including mixtures of other carbohydrates, are being studied to determine whether they can significantly lower the caries potential of the diet.

Antimicrobial approaches include the testing of agents that show promise of inhibiting the cariogenic action of plaque, the bacterial film that constantly forms on the teeth. Intensified efforts will also be made to develop an anti-caries vaccine, admittedly a highly complex and more long-range undertaking. Unlike the majority of infectious diseases, caries confers no resistance to a subsequent attack and does not engender a characteristic antibody response. The reason is that the areas most often involved, the crowns of the teeth, are physically isolated from the most common source of antibodies, the blood-vascular system. Since the tooth is bathed in saliva, immunization through the secretory system would appear to offer a better approach than the blood-vascular system.

As part of the effort to improve delivery and acceptance of caries prevention measures, more study is planned in health education and motivation, as well as of techniques for predicting costs and benefits of new programs.

Periodontal and Soft Tissue Diseases

Periodontal Disease

As the main cause of tooth loss in adults, periodontal (gum) disease has left in its wake millions of partially or totally edentulous Americans, and the still unsatisfactory nature of artificial replacements forces these individuals to experience a lower quality of life in their later years.

Of the 90 million adults in the United States who retain some of their teeth, 75 million have periodontal disease, and, of these, 30 million have some advanced form of the disease. Although the disease is not usually noticed until after age 30, it is now being found increasingly in teenagers and even younger children. Gingivitis, the early reversible form of periodontal disease, is present in four out of five persons by the time they are 15 years of age. A more advanced state is already evident in about 4 percent of these individuals. Without care, the disease tends to increase in severity with age.

Although patient-applied mechanical hygiene can prevent this disease in a few highly motivated individuals, such methods are ineffective in the general public because they are too difficult to maintain. Moreover, treatment of periodontal disease is time consuming, costly, frequently unsuccessful, and remains essentially unavailable to the majority of the population because of the high cost and the shortage of periodontists.

Since periodontal disease seems basically to be a localized host/parasite disease, it is believed that major research efforts should be directed toward what is happening at the local level in the bacterial plaque and in the adjacent periodontal tissues. Hence, the microbiological, biochemical, and immunological factors involved in the pathogenetic chain of events receive continuing emphasis. These studies encompass the identification of bacteria that form periodontal plaque and attempt to discover the biochemical basis of bacterial adhesion and the nature of microbial, enzymatic, and chemical activities that may cause disease.

Because the principal form of periodontal disease is characterized by chronic inflammation, major focus is on immunopathologic factors. As the result of progress in delineating the pathologic processes, a number of dental scientists now believe that the constant challenge of plaque makes the patient allergic to his own oral microbes, causing an exaggerated reaction in the gingival tissues that results in periodontal disease. As precise knowledge of the sequence of events in the inflammatory response develops through continuing research, it will hopefully be possible to block these destructive processes at a reversible stage.

Further insights for control and prevention may be expected from the systematic, comprehensive efforts of the last few years to identify pathogenic bacteria. It is now becoming clear that different forms of periodontal disease may be caused by different bacteria.

In continuing, concurrent studies of tissue loss, significant new progress has been made in identifying biological mechanisms of alveolar bone resorption in the human host, and in testing chemical substances to inhibit the resorption.

On the basis of new data provided by studies of etiology and pathogenesis, it is expected that increased future efforts can be directed specifically toward developing improved preventive or therapeutic measures.

Oral Cancer

As a small but vital part of the increasing scope and attention given to cancer research, NIDR continues to seek collaboration with the National Cancer Institute to identify opportunities for studies of oral cancer. This neglected problem is particularly important because of its frequent sequelae of facial disfigurement as well as its high mortality rate.

Each year, more than 8,000 Americans die from oral cancer, which accounts for approximately 3 to 4 percent of all the malignancies occurring annually in this country. Oral cancer is most frequently found in men after the age of 40. Lip cancer accounts for about 25 to 30 percent of all oral cancers, while the tongue and floor of the mouth are the next most common sites. Other areas include the gums, cheek, palate, tonsils, lower jaw, and salivary glands. Oral cancers often go unnoticed and undetected because of the absence of pain in the early stages. With early detection and therapy, more than half of all mouth-cancer patients are alive five years after treatment. Early care is also important in avoiding the mutilating effects and psychological trauma associated with more extensive surgery or radiation therapy for advanced oral or facial cancers. In many cases, basic functions such as eating or speaking become problems.

For these reasons, research emphasis will continue to be placed on the development of methods of mass screening for the early detection of neoplastic diseases of the oral soft tissues. There is particular interest in studying the early changes in the mouth which characterize the progression from the benign to the malignant state. In addition, extended virologic and epidemiological studies designed to obtain more information on the causative factors of oral cancer will be encouraged, and studies to determine the mode of action of various carcinogens implicated in oral cancer will be continued.

Oral Soft Tissue Diseases

Each year the oral mucous membranes and salivary glands of over 40 million Americans are affected by ulcerative disorders and other diseases. More than 50 percent of the population is affected by recurring ulcers of the oral soft tissue.

The two major ulcerative disorders are aphthous stomatitis (canker sores) and herpes simplex infections (cold sores or fever blisters). Many affected persons endure recurrent discomfort. Effects range from annoyance through severe pain to possible death in newborn infants, young children, and certain adults.

Of all the soft-tissue ulcerative disorders in the mouth, only the cause of herpetic lesions is clearly established. The first exposure to the herpes simplex virus, usually in early childhood, produces a primary herpetic infection that can be quite severe. Following this initial attack, the individual becomes a carrier and may suffer repeated, secondary herpetic infections about the nose, lips, and oral tissues. These recurrences, commonly known as cold sores or fever blisters, frequently follow lowered physical resistance, illness, trauma, or emotional stress.

In addition to causing fever blisters or cold sores, type 1 of the herpes virus can be very serious under certain circumstances and cause brain damage and death. It also frequently invades the skin following burns or eczema, and attacks the eyes of perhaps as many as 500,000 people in the United States, often resulting in blindness. Type 2 of this virus attacks the urogenital system of an estimated 100,000 persons a year, and might be linked to cervical cancer.

Also, recent studies of human subjects susceptible to herpes infection showed that herpes simplex virus causes a depression in the cellular immune defense mechanism of the body.

At present, there is no cure for these viral infections, and methods available to control their severity and the discomfort they cause are at best unsatisfactory.

Significant advances have been made in viral immunology in understanding the structure, chemical composition and biosynthesis of herpes simplex virus. Intramural researchers at NIDR have recently shown that, in addition to antibodies in serum, an immune reaction associated with certain white blood cells appears to be extremely important in the defense against herpes simplex virus. It is now believed that a combined action of these two components of the immune system is necessary to defend the host and stop the spread of infection.

NIDR believes that better diagnosis, control, and prevention of herpes simplex virus infections can be realized within a foreseeable period through more intensified research. The recent significant advances in viral immunology may well provide new approaches to the treatment of herpes simplex virus infection and may offer clues for the development of an effective vaccine. Current efforts include analysis and purification of antigens produced during active infections with this virus. Different chemotherapeutic agents will also be tested to find more effective ways of treating those patients who are already suffering from this infection.

Like herpes simplex, aphthous ulcers, known as canker sores, are a common affliction. However, no specific causal agent, viral or bacterial, has yet been found, although one bacterial strain has been suspected. These lesions usually start in the first or second decade of life, develop inside the mouth, and affect between 20 and 50 percent of the population. Frequently, the severe pain they cause makes eating or drinking extremely difficult.

There is an association between the frequency and severity of the lesions and a number of environmental factors, such as overexposure to sunlight. Sometimes abrasions from hard food or from bristles on a toothbrush, allergies to foods, and endocrine disturbances seem also to trigger attacks. Another predisposing factor is emotional stress. For example, the disease is more likely to develop in college students during examination periods than during vacation.

Identification of the still elusive cause of aphthous ulcers will require an expanded research program by virologists, bacteriologists, and immunologists. Once the etiologic agent has been identified, steps can be taken to devise more effective treatment procedures and ultimately preventive measures.

In the meantime, the causative agent is being sought through studies of tissue cultures and electron microscopic examination. Concurrently, the effectiveness of acromycin in the treatment of the acute aphthous lesion is being evaluated.

The nature, structure, and function of the major salivary glands and their secretory products represent another important area of study. Normal salivary gland function is a prerequisite of oral health. Improper functioning leads to ecological imbalance, and rampant caries, gingivitis, or dry mouth can develop. There may also be disruption of digestive and other physiologic processes. Because salivary secretions contain protective antibodies, saliva may act as a first-line defense against infection.

As a result of studies on the precise nature of the chemistry of saliva, it is now possible to identify and measure special salivary antibodies and certain basic proteins. New evidence indicates that these special antibodies of the immunoglobulin A system (the only blood antibodies normally found in saliva) help prevent local oral disease by keeping specific bacteria from adhering to the oral mucous lining. Future research will include attempts to show a relationship between the levels of salivary antibody and the presence or absence of oral disease, and to determine whether elevating the levels of salivary antibody in experimental animals will enhance resistance to disease.

Restorative Materials

Until oral diseases can be completely eradicated, practically every person during his lifetime will need some type of restorative material to repair damaged tissues, to preserve the integrity of the mouth, and to restore both function and esthetic appearance. Whether the need arises from tooth loss, congenital malformation, oral cancer, or oral-facial injury, research continues to develop longer lasting, more easily applied materials and improved techniques for such restorations.

The major emphasis in recent years has been on restorative materials for treating carious lesions and on adhesive sealants. Although the hope persists that molecular bonding might be induced between the tooth material and a combination of polymers, current emphasis is turning toward developing better mechanical bonding at the microscopic level. This effort is being primarily directed at adhesive-composite restorative materials and improved tooth coatings to prevent caries. An important step forward was the development, supported in part by NIDR, of a plastic binder that is the basis for all composite fillings on the market today, as well as the highly promising plastic sealant currently being tested against tooth decay. Efforts are also continuing to improve amalgams as well as other restorative materials.

Greater emphasis is not being placed on implantology and maxillofacial prostheses. A number of candidate materials, designs, and procedures are currently available and are being evaluated in animals for possible use in clinical trials with humans.

The requirements for successful dental implants are perhaps even more difficult to satisfy than medical implants completely sealed inside the body's tissues. For example, dental implants must not only penetrate into bone, but must also be compatible with the overlying and adjacent soft tissue, and with the complex environment of the mouth cavity, where infection is an ever-present danger. Thus, the development of a successful dental implant offers a uniquely difficult research challenge.

While single-tooth implants of plastic have been studied in animals for some time, attention has focused more recently on the possible use of ceramics, glass, and carbon metals, as well. Experimental studies are now assessing the influence of the chemical composition of the tooth implant, as well as the tooth design, including such factors as grooves, slots, and porosity, on implant acceptability.

Suitable artificial dental implants would be a boon to the millions of partially and fully edentulous Americans by serving as replacements for individual teeth or as anchors to hold prosthetic appliances.

In the area of maxillofacial prostheses, NIDR is supporting the development and testing of materials specifically for use as artificial skin in humans.

Craniofacial Anomalies

Malocclusion

Malocclusion is the primary developmental defect in the craniofacial region. Severe malalignment of teeth and under- or over-developed jaws not only cause varying degrees of disfigurement and associated psychological problems, but may also lead to faulty chewing and speech and predispose to periodontal disease.

In the United States, about one-third of school-age children suffer from malocclusion severe enough to require orthodontic treatment. Over $500 million is believed to be spent annually on orthodontic treatment, and yet the vast majority of the children requiring such treatment do not receive it.

A greater understanding of the growth and development process is essential to prevent malformation from occurring in the individual. The development of simpler ways to prevent crowding and to straighten teeth would enable the practitioner to more efficiently treat most types of malocclusion, thus bringing care within the reach of millions now untouched. Toward this end, NIDR supports clinical research on craniofacial growth and oral function and laboratory studies on the basic cellular response to orthodontic treatment.

Recent studies in which jawbone growth has been modified in subhuman primates by innovative means suggest that it may now be possible to understand local causes of malocclusion and the pathogenesis of the deformity. With this knowledge of how jaw growth may be influenced or controlled, future studies on subhuman primates may soon permit clinical research on interception and prevention of some forms of malocclusion by applying these procedures at very young ages.

Studies have shown that the primary factor in malocclusion is the discrepancy between jaw size and size of the teeth. Control of jaw size and jaw width, therefore, may reduce the impact of this defect.

Although much more basic work will be required before methods can be developed for early diagnosis and improved therapy for malocclusion, significant new insights are being contributed by research on growth prediction, biomechanics, and treatment evaluation.

Cleft Lip and Palate

Of the common craniofacial anomalies, clefts of lip and palate, which develop in the embryo, cause the most severe deformity and impairment of function. A defective palate makes it difficult to speak, breathe, or swallow properly and renders the victim more susceptible to respiratory infections, hearing problems, and psychological disorders.

Cleft lip/palate constitutes 13 percent of all reported birth anomalies. It occurs about once in every 700 births, affecting 6,000 to 7,000 newborn babies each year. Habilitation of a cleft patient involves the coordinated effort of many specialists and costs about $14,000 through the eighteenth year. The annual expenditure for those receiving treatment and habilitative services is estimated at $100 million.

Support for interdisciplinary research in corrective treatment has been well rewarded by development of procedures to enable the affected individual to take a useful and productive position in society. However, further study, necessarily extending over a period of time, is required to determine the best surgical and habilitative procedures and the best timing of treatment. Unfortunately, the end results of treatment are still somewhat less than perfect for many reasons. In addition to defects in appearance and speech, patients frequently are ill-prepared for adult life from a psychological and social standpoint.

While research continues on the habilitative aspects, emphasis is now also being placed on etiologic factors. Study findings indicate that clefts usually result from a number of predisposing genetic or environmental factors, or both, which are operative early in embryonic life. Cleft palate without a cleft lip has also been shown to be a different condition from cleft lip with or without cleft palate.

Illustrative of work done at the cellular level, studies are examining whether fluid retention and certain drugs upset the work of energy-converting enzymes during pregnancy and contribute to animal clefting. Too little thyroxine, vitamin imbalance, stress, toxoplasmosis, and viral infections are some factors suspected of contributing to clefting.

A new technique has made it possible to directly observe the developing embryo and thus obtain better control of variables of the animal model experiments and improve the study of mechanisms of teratogenesis. One finding obtained with this technique indicated that cortisone produces cleft palate in mice by reducing neuromuscular activity, thus hindering the normal displacement of the tongue from between the palatal processes.

Through other advances, the embryonic migration of labeled cells from the neural crest region may now be followed, helping to time more precisely the various stages of cellular differentiation and migration in craniofacial development.

Continuing population and family studies, as well as fundamental research in developmental biology, may be expected to further elucidate the problem of clefting.

Other Craniofacial Malformations

Concurrent with these efforts, NIDR is beginning to direct more research to a broader spectrum of craniofacial malformations. Less common, but equally disfiguring anomalies include such deformities as a misshapen or partially missing lower jaw or ears; eyes which are excessively set apart and prevent normal vision; and a cranium with sutures that do not grow, thus causing damage to the growing brain and a distortion of the facial structures. Usually, the anomaly includes a combination of these deformities and perhaps malformations of other aspects of the body, such as feet and hands.

This broadened scope of NIDR research is timely in view of the recent breakthrough in surgical treatment of severe craniofacial deformities. The new radical surgical procedures, however, have introduced a host of problems related to future form and function which require extensive research.

Pain Control and Behavioral Studies

Pain is a central issue in the practice of dentistry for two primary reasons. First, pain is intimately associated with almost all dental corrective, surgical, and restorative procedures, and even the fear and anxiety associated with anticipation of such treatment creates major difficulties for the patient and dentist. Second, members of both the medical and dental professions are frequently called on to treat a variety of pain syndromes localized in the facial region, such as facial neuralgia, glossodynia, dysfunction of the temporomandibular joint, oral cancer, recurrent stomatitis, and others.

Public demand for relief from pain related to dental treatment is reflected in the growing use of both local and general anesthesia. Each year, in the United States alone, some 50 million dental carpules (2 cc doses) are used to produce local anesthesia. About 5 million persons a year receive general anesthesia on an ambulatory basis, the great majority in private dental offices. In fact, over one-fifth of all general anesthetics administered in the United States are used in conjunction with dental treatment.

Since the etiology and mechanism of action of most oral-facial pain syndromes is largely unknown, treatment is empirical and usually inadequate. Because this area has been so grossly neglected, a substantial amount of clinical study and research in relevant basic sciences will be required before hope for improved care and relief can be held out to afflicted persons.

In addition to deficits in vital knowledge necessary to deal with the complex physiological, pharmacological, and behavioral treatment problems of dental and facial pain, the area of dental anesthesiology is particularly underdeveloped in comparison with its medical counterpart.

More also needs to be known about techniques in which people can remain conscious and cooperative during painful dental operations and yet be rendered amnesic of the overall unpleasantness of the procedures. These techniques are not yet standardized, and there is need for much additional research to further establish tests for the selection of the best drugs or combination of agents as well as the overall management of the patient.

The search for more acceptable means of controlling pain and relieving anxiety will also capitalize on new modalities of pain control not involving drugs. It will include further studies of electrical methods, acupuncture techniques, and other physical means of pain control.

In view of the extreme shortage of adequately trained basic and clinical investigators, NIDR is cooperating with the American Dental Association to foster training and research in pain control in dental schools. Plans call for the establishment of discrete anesthesiology and pain control research centers in selected dental schools. In addition, because of the complex, multifaceted nature of the pain problem involving neurophysiological, pathological, and behavioral aspects, efforts are underway to develop an integrated approach to oral-facial pain research and training in non-dental environments.

Dental Research Institutes (Centers)

A critical examination conducted several years ago showed that education and research in the sciences relevant to oral health were not advancing fast enough to bring the full potential of modern science to the benefit of persons threatened with oral disease. In order to accelerate the development of scientific knowledge needed to support dental care, dental research, and dental education, NIDR established a special program to support a limited number of centers or institutes in university environments. Five such centers are now in operation at the Universities of Alabama, Michigan, North Carolina, Pennsylvania, and Washington.

Initiated seven years ago, the program seeks to attract the knowledge and skills of scientists in disciplines not previously involved in dental research. The institutes build on and extend existing institutional research strengths, provide for participation of multiple disciplines, facilitate the cooperation of a broad range of biological, physical, and social sciences in the study of problems of common interest, and interact with the education program of the parent university.

Although the focus of each institute varies, collectively they embrace research efforts covering the broadest spectrum of oral-facial disease. Thus, fundamental and applied science programs at the Alabama institute relate to the etiology, prevention, and treatment of oral diseases with special emphasis in the connective tissue area. The program at Michigan is concentrated in the areas of periodontal disease and caries, viral diseases of the oral cavity, and growth and function of the masticatory apparatus. The North Carolina center is conducting research in growth, development, and function of the craniofacial region; biomaterials; and pain control. Studies of periodontal disease, caries, and the herpes simplex virus are among the research projects at the Pennsylvania center. The center at Washington emphasizes research in periodontal disease, salivary secretions, and nutrition.

This network of dental research centers not only contributes new knowledge but also provides stimulating environments for training researchers and teachers. A deliberate effort is also being made by these centers to encourage greater collaboration with other institutes, regardless of geographic boundaries, and most particularly schools of dentistry.

An attempt is now being made by NIDR to evaluate the institute/center concept as an instrument of science policy through determining conformance with guidelines set for the centers, achievement of their original objectives, and their effectiveness in relation to other forms of support.

Training

Traditionally, dentistry has lagged behind medicine in the numbers of research-trained investigator-educators. Despite the substantial impact of NIDR training programs in developing a cadre of dental researchers and in improving the quality of dental education and practice, there continues to be a serious deficit of scientific manpower in this field.

During the last five years NIDR staff has held more than 60 formal meetings with scientific leaders throughout the world in attempts to determine projected needs for research personnel to study oral diseases. Through such outreaches, including advisory committee meetings, workshops, training directors' conferences, and other consultations, NIDR has been able to identify specific manpower needs in a number of different areas. Projections are based upon a consideration of promising research, the number of qualified individuals already active in the research, and the potential for redirecting active researchers into more oral disease-oriented research with minimal additional training. Two types of researchers, one highly specialized and the other more broadly trained, are envisioned for future work. It is expected that the ratio of the specialized researcher to the broadly trained scientist would approximate 4-5 to 1. In particular, there continues to be a dearth of clinical scholars with training in basic disciplines.

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NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Introduction

Few of the basic industries by which modern civilization is sustained are without profound impact upon the human environment and the quality of human health. It has been predicted that as much as 80 to 90 percent of future health disorders will be related to hazardous chemicals and physical factors in our work and social environments. Regardless of whether one accepts the validity of such estimates, the gigantic proportions of the problem are clear. Thus, the National Institute of Environmental Health Sciences (NIEHS), located in the Research Triangle Park, North Carolina, conducts and supports fundamental research toward the solution of environmentally related health problems. NIEHS seeks to identify those factors in the environment that can affect man adversely; to understand the mechanisms of interactions at the molecular and cellular levels that are eventually manifested as overt diseases; and to provide the scientific basis for corrective and preventive medicine. Particular attention is given to the effects of environmental agents acting over long periods, the mechanisms and consequences of multiple factors operating concurrently, and the basic characteristics of human physiology which influence susceptibility to, and the course of, environmentally related diseases.

While the public is the ultimate beneficiary of knowledge developed by the NIEHS, the more immediate beneficiaries are other agencies and individuals who have protective and health care delivery functions. Close liaison is maintained with other governmental agencies concerned with environmental components of cancer, mutagenesis, reproduction, child health and development, heart and lung diseases, and mental health. The findings are also made available to those professionals concerned with clinical aspects of diseases with environmental components in specific social and work situations.

Because of the number of factors involved and the complexity of environmentally related disorders, research resources and manpower are developed in a number of fields and disciplines, and several mechanisms are used to implement research programs. Approximately one-third of the resources are applied to research conducted within facilities at the NIEHS and through contracts, which extend intramural capabilities. These activities focus upon aerotoxicology, mutagenesis, teratology, reproductive toxicology, and general toxicology and pharmacology, with complementary research and services in chemistry, biometry, and statistics.

The remaining resources are utilized for support of University-based Centers and program projects and for individual research projects, career development awards, fellowships and other mechanisms of manpower development. The University-based Centers integrate the efforts of scientists in several traditional disciplines within the University and foster application of expertise across disciplinary lines to environmental health problems. Collectively, they provide strong capabilities in basic and applied research in chemistry, biophysics, cell biology, genetics, physiology, pharmacology, toxicology, pathology, psychology, epidemiology, biostatistics, behavioral sciences, nutritional sciences, occupational medicine, and chemical and environmental engineering.

To an equal or greater degree, individual research grants bring the talents of outstanding scientists throughout the nation to bear upon environmental health problems and involve the widest possible range of professional disciplines. Dual considerations in the award of such grants are scientific excellence and relevance to environmental health.

Regardless of the implementation mechanism, continuing efforts have been made to maintain an effective blend of fundamental and applied research. Thus, broad investigations on a national and international scale are conducted under four programs dealing with: (1) Etiology, (2) Pharmacology and Toxicology, (3) Pathogenesis, and (4) Mutagenesis and Reproductive Toxicology.

Etiology of Environmental Diseases and Disorders

The central objective of the Etiology Program is to establish causal associations between human diseases and environmental factors. The long term aim is to provide a sound basis for management of technology consistent with the view that public health has the first priority in human affairs.

Chemical Factors

Pesticides. As already indicated, few major industries are without impact upon the health of employees and the public at large. In agriculture alone, several million tons of toxic chemicals are purposely released each year into the environment to control crop and livestock pests and diseases. Some of these, particularly thiophosphate insecticides, are nerve poisons rivaling war gases in toxicity, and they have caused scores of deaths among workers involved in their manufacture, formulation and application. Chlorinated hydrocarbons, though less toxic, may persist for many years in soil and water, and their possible significance in the future well-being of man is sometimes seen in the prophetic decline of wildlife and marine populations. Moreover, recent work has shown that a number of these compounds induce cancer in experimental animals.

Ongoing studies continue to reveal heretofore unrealized effects of individual and combined pesticides in mammalian systems. Comparative studies on the effects of carbamates, organophosphates, and chlorinated hydrocarbons on the nervous system, show that, though there are differences in the mode of action of the major classes of neuroactive pesticides, the compounds may induce various reproductive and behavioral disturbances, and, in some cases, cancer. Thus, full understanding of the ramifications of pesticide usage in human health requires much further careful work.

Of even greater impact on the environment than agriculture is the chemical industry--a major cornerstone of modern technology. An estimated 400 new compounds are brought into commercial production each year alongside several hundred thousand already in use as industrial intermediates, preservatives, pesticides, pharmaceuticals, polymers, heat exchangers, insulators, adhesives, food and fuel additives and a host of others.

Increasingly, efforts are being made to test these compounds for biological effects before they are widely distributed. However, even if adequate manpower and facilities were available for comprehensive testing of new compounds, the task of evaluating compounds already in use would be virtually insurmountable. Thus, etiological relationships are often established on the basis of representatives of classes of compounds. While such an approach is not without shortcomings, experience shows it to be useful as a first approximation of risk.

The following are examples of areas in which the etiological role of classes of agents is being investigated.

Polychlorinated biphenyls (PCBs) have been utilized for more than 40 years in a wide range of industrial applications because of their heat resistant characteristics. They have been used as electrical insulating fluids for capacitors and transformers; industrial fluids for hydraulic, gas-turbine, and vacuum pumps; and as plasticizers. The PCBs are extremely stable compounds which are degraded slowly in the environment, and although acute toxic effects of the compounds have been identified, definitive aspects of subacute and chronic toxicity for man are still unknown.

Phthalate esters have been used for three decades as additives in plastics to make them flexible. Accordingly, they have a wide use in such materials as food wraps, drinking containers, blood storage bags, and plastic upholstery. Concern regarding their potential hazard to human health developed when an NIEHS grantee showed that they migrate from plastic containers into stored blood and may be introduced in significant quantities into patients during blood transfusions.

Approximately a billion pounds of phthalates are produced annually. The esters have been identified in crude oil, water, fish, fish meal, and cotton seed meal, and as vapors from new car interiors. NIEHS supports basic research on the major esters through the grants program, and has sponsored a conference to facilitate exchange of information among industry, government agencies and individual scientists.

Chlorinated bisphenols. These compounds, especially hexachlorophene, have been widely used as antiseptic agents in soaps and cosmetics. Although they are considered safe from the standpoint of percutaneous toxicity, they are powerful hemolytic agents and extremely toxic to mammals. Convulsions and temporary neurological disorders have been reported in burn patients treated topically with hexachlorophene. Studies on distribution patterns, metabolism, and mode of action of the compound show it to be highly persistent in the environment and slowly metabolized in the body. Significant amounts were found to accumulate in the lungs of newborn rats, suggesting substantial hazard in infants, since metabolic defenses in the newborn are poorly developed.

Vinyl chloride and other plastic intermediates. A number of chlorinated monomers used extensively in polymer and plastics synthesis have been implicated in liver toxicity and carcinogenesis. Workers exposed to as little as five ppm of vinyl or vinylidene chloride in air are reported to show evidence of hepatic injury and an unusual cancer of the blood vessels. Recent studies conducted by NIEHS grantees show that the mechanism and manifestations of toxicity are generally similar for compounds of this group. Strong measures are now being taken by regulatory agencies to limit exposure to these agents in occupational environments, and basic research on the toxicological and pathological aspects of the problem is being accelerated.

Fluorinated Hydrocarbons. Considerable concern exists about the toxicity of freons used as refrigerants and aerosol propellants and of fluorinated hydrocarbons employed by fire fighters. Tests conducted intramurally on normal and myocardiopathic hamsters suggest that freons can adversely affect animals and perhaps humans with cardiovascular disease. Epidemiological studies of firemen who are exposed to other fluorinated compounds are in progress but definitive long-term results are not yet available.

Airborne Fluorides. The hazards of fluorides released in large quantities from aluminum refining plants have been of concern for many years. Data developed by grantees, show that mottling and banding of incisor teeth and discoloration of other teeth occurs in humans who drink water with a fluoride content of 1.5 to 2 ppm. At higher levels, more profound effects are seen, including abnormal growths on the surface of certain bones (exostosis). At persistent levels in the range of 5 to 30 ppm, the life span of exposed animals is reduced by about 25 percent.

Industrial Solvents Grant supported research has added further to an understanding of the toxic action of benzene and other solvents. Benzene depresses incorporation of ^{59}Fe into an early precursor of the erythrocyte in the bone marrow. Through appropriate time correlates in erythrocyte formation, the cell type involved in benzene toxicity can be precisely identified.

Metabolic studies suggest that only one major metabolite; e.g., phenol, is formed from benzene in mammals, and this is rapidly excreted in the urine as sulfate and glucuronate conjugates. Intramural inhalation studies show that toxicity can be reduced substantially by compounds that induce hepatic microsomal oxidases, suggesting the possibility of protecting exposed individuals through manipulation of drug metabolizing systems.

Heavy Metals. Effluents of heavy metals, particularly cadmium and mercury from industrial processes and lead from paints and gasoline engine exhausts, are being investigated intensively. Cadmium enters the environment as a major by-product of numerous industrial processes and in consumer products. Renal damage has occurred in exposed alkaline battery workers, and use of cadmium in food containers with acidic foods has led to cases of intoxication. Several reports have indicated that cadmium may cause abortion in the mouse and teratogenic effects in the hamster. In addition, it has been established that compounds of cadmium are potent immunosuppresants, cause substantial elevation in blood pressure, and affect male reproductive capability. Present studies are aimed at establishing the physiological and cellular disorders associated with these effects.

Mercury is a particularly hazardous element, not only because of its high, broad-spectrum toxicity, but also because elemental mercury and inorganic mercurials are converted into alkyl mercury by microorganisms and can cycle indefinitely in the food chain. Higher than allowable levels of methylmercury have been found in some fish, fowl, game, foodstuffs and water. NIEHS scientists have developed a highly reproducible model of acute alkyl mercury intoxication (Minamata disease) in the adult rat, which should be extremely useful to other investigators studying the pathogenesis and treatment of methylmercury intoxication.

Primarily through its use in gasoline and paints, lead is also universally distributed, presenting problems similar to those associated with mercury. Extensive studies show clearly that the most devastating effects of mercury and lead at environmental levels involve the nervous system. Moreover, the fetus and newborn are many-fold more susceptible to intoxication than the adult. Studies in experimental animals and in children indicate that both substances are teratogenic at high levels and may induce aberrations in behavioral patterns and learning capacity at extremely low levels that produce undetectable biochemical or morphological lesions in the nervous system. This has added a new dimension to the problems of plumbism and mercurialism and suggests that older methods of assessing the hazards of mercury and lead may be inadequate.

Combustion by-products and ozone. Significant new etiological relations of oxidant air pollutants have been found by NIEHS grantees. For example, exposure to ozone increases carbonyl compounds in the blood in experimental animals. Such compounds are presumed to be important as secondary, if not primary, factors in the progression of ozone-induced lung damage. NO_2 inhalation was found to accelerate lipid peroxidation and formation of age-related lipofuscin pigments. Moderate doses of vitamins A and E counter the effect, suggesting that high levels of these vitamins and perhaps other natural antioxidants may be useful in preventing lung damage induced by low levels of atmospheric oxidants. Further studies on SO_2, which take on added significance with increased use of coal and low grade petroleum, show that the gas reacts with disulfides in the blood plasma to yield stable S-sulfonates. Blood thiolsulfonate levels increase in proportion to inhalation of SO_2 and have a mean half-time of about three days. The significant aspect of the reaction is that the products circulate to all parts of the body where they can react with vital enzymes and DNA. Studies are currently in progress to determine the nature of the proteins involved in thiolsulfonate reactions and the role of such reactions in chronic physiological disorders.

Carbon Monoxide is the most nearly ubiquitous gaseous toxicant. Population groups of greatest concern include cigarette smokers, workers in automobile traffic control, automobile mechanics working in closed buildings, fire fighters, certain factory workers and individuals in substandard homes with improperly vented heating devices.

Information from fundamental and epidemiological studies leaves little question that CO is an agent with considerable impact upon the human population. It may contribute to fatty accumulations in the blood and in arterial and heart muscles, aggravating preexisting cardiovascular diseases. Thus in addition to the long recognized action of CO as an acute toxin, it may also be an insidious etiological factor in long-term degenerative diseases.

Industrial dusts. Many of the more insidious diseases associated with environmental factors are those induced by industrial dusts. Such diseases generally occur in the lungs, although the upper respiratory tract and the gastrointestinal tract are often primary or secondary sites. Major sources of dusts are mining, textile, plastics, agricultural, and building industries, which give rise to characteristic diseases such as coal miner's pneumoconiosis, asbestosis, cancer, brown lung, farmer's lung, emphysema and chronic bronchitis. Pneumoconiosis alone afflicts about 100,000 workers in the coal mining industry, and current shortages in world supplies of oil will undoubtedly result in renewed activity in coal mining and insulation industries, which will bring additional manpower into dust-laden environments.

Epidemiological studies on asbestos have revealed heretofore unrecognized hazards associated with asbestos inhalation. In addition to lung scarring (abestosis) in asbestos miners, the fibers also increase the risk of carcinoma of the lungs and gastrointestinal tract and mesothelioma of the pleural and peritoneal linings. The diseases may take 30 years or more to develop and may occur in individuals whose exposure was of relatively short duration. Moreover, they may develop in workers whose exposure to asbestos is much less intense than that of asbestos miners. Increased cancer has been documented among insulation and other workers in the building trades, and very recent studies show that the probability of cancer and asbestotic fibrosis is substantially greater--sometimes as much as 50-fold--among insulation workers who are also heavy smokers. This raises serious questions of general population risks in urban areas where the content of asbestos in the air is high, along with a host of other lung irritants, and has intensified quantitative studies on asbestos in relation to time, dose and combined factors.

The health implications of industrial dusts have spurred studies on the basic aspects of lung physiology and airflow dynamics. Airflow model studies on wood dusts from woodworking shops have demonstrated the sites of deposition of wood particles and made possible correlations of the deposits with nasopharangeal cancer, one of the more common afflictions in the woodworking trade. Similar correlations have been made between the incidence of deep lung cancer, emphysema and bronchitis and the nature and size of particulates.

Studies on alveolar macrophages have added substantially to our understanding of the role and capacity of these cells in protection of the airways against particle impaction and airflow restriction. At the same time, evidence is accumulating that destruction of macrophages by environmental agents may result in release of lysosomal enzymes which attack sensitive, reactive lung surfaces and initiate lung lesions and tissue degeneration.

Natural toxins. Natural toxins with which man may come into contact come from a wide variety of living organisms, including higher plants, lower animals, insects, fungi, algae, dinoflagellates, and bacteria.

New toxins were discovered recently in sweet potatoes infected with the fungus *Fusarium solani*. The toxins cause severe edemagenesis in the lungs of animals that eat infected potatoes. At least four compounds making up the "lung edema factor" have been isolated and identified by grantees. In addition to their lung edemagenic properties, three of the compounds are nephrotoxic in mice.

Storage of human foodstuffs and livestock feed is often accompanied by fungal infestation. Metabolic products of certain fungi, when ingested with these foods, have been shown to cause serious toxicoses and cancer in animals. There is growing evidence that *Alternaria* spp., often associated with agricultural commodities, may rank in importance as a potential hazard in foodstuffs with the better known toxigenic *Penicillium*, *Aspergillus*, and *Fusarium* spp. Several metabolites of *Alternaria* have been isolated and identified or partially characterized. Some are toxic to a wide spectrum of microorganisms and mammals, causing a variety of toxicoses, including brain damage.

Grantees have shown that zearalenone, a metabolite of the fungus *Fusarium*, induces absorption and fetal resorption when fed to rats. Further work on several species of toxigenic Penicillia have demonstrated by-products capable of producing bronchiolar and alveolar adenomas and adenocarcinomas in mice. In addition, certain of the test species produce phototoxic syndromes in mice exposed to sunlight, such as erythema, edema and necrosis of the muzzle, ears, paws and tail. Keratitis and blindness occurred in some animals. Other species were found to produce toxicity characterized by ballooning degeneration of hepatocytes and nuclear hypertrophy in both hepatocytes and renal tubular cells.

Work on purified ochratoxin A, a carcinogenic metabolite from *Aspergillus ochraceus*, has resulted in the finding that the compound will induce hepatomagenesis in young rainbow trout through exposure of the eggs for only one hour prior to hatching. This is one of the first demonstrated instances of cancer induced in the embryonic state.

Miscellaneous Carcinogens. Epidemiological studies of environmentally related cancer have been underway for several years. Previous indications of prenatal X-ray as an etiological factor in childhood cancer have been confirmed. Work on the association between coffee drinking and bladder cancer was extended and new data suggest that earlier findings of increased bladder cancer risk among coffee drinkers will be confirmed. Retrospective cohort studies of retired leather workers confirms previous indications of increased bladder cancer in this group. These studies, like those dealing with asbestos and smoking, indicate the complexity of social and industrial factors in all walks of life that may have a direct individual or combined effect on many types of cancer.

Physical Factors

The influence of physical factors in the environment on the human body have long been recognized. The effects of light, both visible and ultraviolet, in circadian rhythmic processes and in cancer of the skin are recognized but still poorly understood. More recently, there has been an increase in concern about the effects of heat, noise, microwaves, and radioactive nuclides and their interactions with chemical and infectious agents and disorders of genetic origin.

Heat. For apparently the first time, grantees are attempting to assess heat stress in women in relation to hormonal and related physiological changes during the menstrual cycle. The studies include females at all stages of life from prepubertal through postmenopausal. Research is being continued also on the more general aspects of heat to provide a basic understanding of man's response to his thermal environment. Much of the effort is devoted to physical characterization of the thermal environment in terms of a useful index of heat stress and of heat strain. The ultimate objective is to determine the quantitative relationships between the voluntary and involuntary actions of man in response to heat in order to determine optimal conditions for rest, work and a number of more subtle physiological functions.

Light. The influence of light on hormonally-controlled processes in mammals is being explored. The studies are concerned with the basic molecular events through which neuroendocrine effects are initiated and carried out. In addition to control of body rhythms through the endocrine system, light was shown to have an influence on the acute toxicity of certain natural toxins, such as aflatoxin and monocrotaline (hepatotoxins). In the case of the carcinogen aflatoxin, either light or riboflavin will enhance acute toxicity, and when the two are combined there is further enhancement. These results indicate the complex nature and the potential importance of light in the action of sensitizing food ingredients in biological systems.

Microwave Radiation. The use of microwave radiation in domestic and commercial ovens, communications, industrial processing, radar, and medical diathermy has greatly increased over the past 20 years. The types and amounts of microwave radiation emanating into the environment has multiplied to the point that the general population is now exposed to a complex, low-level microwave field. Whether this field is hazardous to man remains an unanswered question. Biological effects of microwaves on cells and unicellular organisms have been reported, but information on the mechanisms of interaction between radiation and cells is grossly inadequate.

NIEHS has developed a program to study the effects of microwave radiation on cells and unicellular organisms, and to develop techniques for evaluating the mechanisms of interaction with cellular components, such as DNA, RNA and proteins. Research on the microwave effects on very early stages of development have been initiated also, using the capability of the Institute scientists to experiment directly with fertilized mammalian egg cells and to later implant them in the uterus of experimental animals.

Noise Pollution. The recognition that noise is as much a factor in environmental pollution as noxious gases or contaminated water and soil is a recent acknowledgment. At present, very little is known of the specific or general effect of noise on man's health and well-being. Long exposure to high noise levels can cause permanent loss of hearing, but this only one aspect of the spectrum physiological and phychological effects of noise. It has been established that the developing fetus is subject to many of the same auditory stresses that affect adults, with long-term influences on learning and behavioral characteristics. The etiology of sensorineural hearing loss in young children is, however, frequently obscure. NIEHS has initiated research on noise from infant incubators as a possible factor in the cause of such hearing loss, particularly in premature infants. During the course of these investigations, it was learned that potentiation of the effects of noise and ototoxic antibiotics can occur in pediatric situations.

NIEHS research is concerned also with development of instruments for measuring impedance of the middle ear. Present impedance measuring devices are limited to very low frequencies, are unwieldly, require very precise measurements of ear canal volume and near immobilization of the subject, and are limited as to range of atmospheric pressures that can be tolerated. Once operational, the instrument will be used to develop information about the change in impedance with increased pressure. Work is also progressing on adapting the Zwicker loudness calculation scheme, which measures the loudness of sounds so that annoyance can also be quantified.

Ionizing Radiation. Since it became apparent that potential usage of the atom might result in release of multi-megacurie amounts of fission products, and with the projected increase in use of nuclear fuels for electrical power generation, health effects of ionizing radiation have attracted intense public interest. Sources of radiation exposures include natural background, use of X-rays and radionuclides in medical diagnosis and therapy, industrial and research applications of radionuclides and radiation-producing devices, exposures of workers to radon and its daughter products in underground mining, and exposures of the general population through environmental releases of radionuclides from nuclear reactors and nuclear fuel reprocessing plants. NIEHS researchers have developed a theoretical model which describes the effect of dose rate and turnover time of cells on dose-response relationships. This model provides a basis for experimental work on the main interactions of ionizing radiation with matter. If experimentally verified, the theory will allow extrapolation of dose-effect data to low doses, which was not previously possible.

Environmental Pharmacology and Toxicology

The Pharmacology-Toxicology Program is designed to develop understanding of the principles and mechanisms involved in toxicity of environmental agents. The research is very broad in scope and includes (1) mechanistic studies which focus on factors in the external environment and in the body that alter the toxicity of chemical agents, (2) modes of absorption and transport within the body, (3) the elucidation of the nature and sites of defense systems, and (4) molecular targets associated with visible functional disorders. The ultimate goal of the research is to provide basic understanding of chemicodynamics that will serve as a basis for identification of situations likely to result in dangerous body burdens of toxic agents, and subsequently for maintaining, through environmental management, reasonable safety margins between environmental levels and body levels. Efforts are being made to clarify complex interactions in the body in order to determine the capability of inherent systems to deal with foreign agents. In many cases, interactions between combinations of compounds result in dangerous enhancement of toxicity even at levels at which the individual agents are normally considered to present no risk to man. Such interactions are being identified and assessed for their consequences in relation to long-term health problems and the risk of birth defects and genetic change.

Toxicology

Investigations on the possible role of ozonides and hydroperoxides in ozone toxicity, show that intravenous injection of these compounds into the rat produce marked lung edema and congestion. These findings are in accord with the hypothesis that ozone damage to lung tissue is due to reaction of ozone with lipids to form ozonides or peroxides, which are presumably the agents directly responsible for tissue damage. An important aspect of such studies is the detection of molecular changes in target tissues prior to development of irreversible pathological changes, since therapeutic and/or prophylactic measures at this stage offer the best opportunity for disease prevention or amelioration.

Recent studies show that administration of calcium ethylenediaminetetracetate (CaEDTA) increases lipid peroxidative activity due to chelation of zinc in the liver. Zinc plays a vital role in protection of tissues against toxic metals and gases through a stabilizing effect on lysosomal membranes. Studies on the plasma membranes of several types of cells, including those of alveolar macrophages and erythrocyte ghosts, show that zinc is present in all such membranes and linked to specific macromolecules. In some cases, at least, the protective action appears to be associated with the capacity of zinc to inhibit or limit the peroxidation of lipids in the membranes.

Heavy Metals. A number of grants are being supported on various toxicological aspects of heavy metals. Further advances have been made toward understanding the clinical, pharmacological and biochemical aspects of lead and mercury intoxication. Studies are being conducted to determine the effects of lead on hepatic heme synthesis, cytochrome P-450 content and function, and the activities of the drug and hormone metabolizing enzymes in the mixed function oxidase system to which the heme protein is coupled. This system plays a predominant role in the oxidative transformation of drugs and other foreign chemicals in the liver. Thus, impairment of heme synthesis in the liver comparable to that known to take place in bone marrow in plumbism would be expected to make lead-burdened individuals susceptible to intoxication by a wide spectrum of drugs. This has been shown to be the case in children with frank plumbism.

Metabolism and Toxicity Modifications of Environmental Agents

Numerous intramural and grant supported studies are concerned with metabolism, activation or deactivation, and toxicity enhancement and quenching of a broad spectrum of environmental agents. Such studies are of utmost importance in understanding the ability of the body to cope with foreign chemicals and are related directly to the ability to make sound decisions with respect to environmental and body burdens vs risks to human health. The program deals with pyrethroids, both natural and synthetic, which are among the safest insecticides, degradation of chlorinated hydrocarbons and the toxicology of degradation products, degradative chemistry of organophosphates and methylcarbamates, and a diverse array of other compounds. One purpose of the studies is to find new, safer and more effective ways of controlling pests. The work includes investigations on insect juvenile hormones and their analogues, a variety of thiocarbamate herbicides, and a large number of new insecticidal and fungicidal compounds.

Work by other grantees is primarily concerned with insecticide detoxication mechanisms. It has been demonstrated that the microsomal oxidases, as well as DDT-dehydrochlorinase, two dissimilar enzyme systems, are induced 2 to 20-fold by a variety of compounds, including organochlorine insecticides, phenobarbital, and certain natural and synthetic insect hormones. Induction is generally greater in resistant than in susceptible insects. This suggests that resistant insects possess more genes for detoxification systems than the susceptible ones. This premise has led to major efforts to unscramble genetic factors involved in different types of insecticide resistance and to determine the associated biochemical parameters of resistance. Studies such as these provide basic understanding of the chemical and biological factors that influence susceptibility to poisoning by insecticides. Thus they are expected to be useful in prediction of conditions of susceptibility from species to species and in the development of new pesticides.

Further understanding of the toxicity and fate of various chlorinated hydrocarbons and species differences with respect to susceptibility to chlorinated hydrocarbons is being developed. In the monkey, liver hypertrophy and increased activity of certain enzymes were observed upon treatment with polychlorinated biphenyls (PCBs). However, these changes were not as great as those observed in the rodent and were subject to more individual variation even though the rat tended to develop degenerative changes in the liver less rapidly than the monkey. Thus species differences in susceptibility are not necessarily reflected in degree of liver damage. When the data and observations from these studies are compared with the rather extensive data available for human patients exposed to PCBs in the Japanese poisoning episode of 1968, it is readily apparent that the symptoms and lesions produced by the PCBs in man are much more similar to those in the rhesus monkey than to those in the rat.

Development of tolerance to drugs and other foreign chemicals is part of the defense system in living organisms against chemical overload. Thus it plays an important, though incompletely evaluated, role in man's adjustment to his chemical environment. Adaptive changes have been observed in various neurophysiological and neurochemical systems during the development of tolerance to organic phosphate insecticides. Paraoxon, for example, induces release of acetylcholine which can give rise to several mechanisms of adaptation. These include the return to normal acetylcholine release under repeated paraoxon exposure and adaptive increase in reuptake of acetylcholine. A third possiblity is an adaptive decrease in receptor sensitivity. It was found also that paraoxon partially blocks a mechanism that removes Ca^{++} from the inside of sarcoplasm of muscle fibers and from axoplasm of nerve terminals. Inhibition of the Ca^{++} pump has not been reported before and may be a possible explanation of organophosphorus action not accounted for by cholinesterase inhibition.

Various aspects of interactions between toxicants and other types of chemical agents, including drugs, are also under investigation. Grantees have examined the effect of chronic DDT exposure on pentobarbital intolerance in the rat. Intraperitoneal doses of pentobarbital were shown to produce a significant tolerance in naive rats to DDT which correlated with a significant increase in the *in vitro* rate of hepatic microsomal pentobarbital metabolism. However, after 20 days of barbiturate abstinence the animals exhibited an intolerance to DDT not associated with any change in hepatic enzyme activity. These studies suggest that the intolerance is nonhepatogenic and is probably related to enhanced central nervous system sensitivity not affected by induction of hepatic microsomal enzymes.

Phthalate Esters (DEHP). The major effort in this area has been devoted a study of the absorption, distribution, metabolism, and excretion of DEHP in experimental animals. In the intact animal considerably greater rates of metabolism and excretion of DEHP were seen than might have been expected on the basis of previous liver experiments. Within 1 hour after an IV injection only trace amounts of the ester can be found in the blood. Following oral administration, the total dose can be accounted for almost entirely as metabolites in urine and feces. These results strongly suggest that the absorption of DEHP is rate-limiting relative to metabolism and excretion so that as soon as the compound is absorbed, it is readily metabolized and excreted.

Aflatoxin Metabolism. Further studies on the toxicity and metabolism of the important fungal metabolite aflatoxin are being carried out to determine if the pathways of metabolism and mode of excretion of aflatoxins by humans are the same as those in experimental mammals. The O-demethylated derivative of aflatoxin is a major metabolite and excretory product of rats and monkeys receiving aflatoxin. Although production of very small quantities of the metabolite could not be ruled out due to the necessity of limited intake, no evidence was found for the derivative in the urine of human subjects. The methodology used was capable of detecting the free phenol or the sulfate or glucuronide conjugate. Thus the findings suggest that human metabolism of aflatoxin probably differs from that of the rat or monkey.

Detoxication of Metals. Despite the fact that heavy metals are not destroyed and are often retained in the body, there is growing evidence of effective, inducible mechanisms for detoxication of, and development of tolerance to, the various toxic ions.

Several studies are currently being conducted on the induction of metal binding proteins, particularly metallothionein, and the localization of metals in subcellular components, such as chromatin, following exposures to sublethal concentrations of cadmium, copper, and mercury. Results thus far indicate that both cadmium and mercury elicit increased production of metal binding proteins and efforts are being made to isolate and characterize the proteins and to develop suitable immunological methods for their detection in tissues and cells.

Other studies indicate that metallothionein is probably only one of several important proteins in metal binding and detoxication. Four mercury-binding proteins have been found in liver and kidney, only one of which appears to be metallothionein. Work is in progress toward further characterization of the other proteins.

Test Systems. The development and improvement of model test systems is an important and necessary concern in environmental health research. NIEHS has made major strides in developing such test systems for work in the areas of carcinogenicity, mutagenicity and teratogenicity, as well as on other interactions of chemicals.

Parallel advances are being made in analytical methodology. A new instrument was developed which will detect 0.5 parts per trillion of the potent teratogen dioxin in cells and tissues. The instrument and principles on which the procedure is based can be applied to analysis of other chlorinated compounds for which methodology was previously inadequate. New procedures have also been developed for the detection and quantification of heavy metals and asbestos and other particulates in body tissues and in the environment.

Environmental Pathogenesis

The Pathogenesis Program focuses upon the details and time sequence of molecular and cellular events that eventually culminate in recognizable diseases and endpoints upon exposure of individuals to toxic environmental agents. Diseases of the pulmonary and cardiovascular systems, the liver, kidneys, reproductive system, digestive tract, the central and peripheral nervous systems, and degenerative disorders of complex and long-term etiology have been documented and related to one or more environmental agents. Additionally, the program is intended to clarify the interactions through which environmental agents play a secondary or ancillary role in the progress of degenerative disorders. Knowledge of initial or very early molecular and cellular lesions and understanding of their role in pathological endpoints offers the best hope, apart from prevention of toxic exposures, for detecting and countering the development of diseases before damage in target organs become irreparable.

Neuropathology

Many environmental agents of primary concern, particularly heavy metals and insecticides, have been shown to affect the central and/or peripheral nervous system and behavioral patterns in experimental animals. Thus a number of projects supported through the grants program have focused upon neuropathology.

Insecticides. Grantees have established that DDT, dieldrin and certain other organochlorines produce changes in the central nervous system (CNS), culminating in convulsions at high doses. Through analysis of evoked responses, it was shown that a major effect of dieldrin is to selectively increase cortical responses to sensory, transcallosal and direct cortical stimuli. Massive cortical cell discharge accompanies the enhancement of evoked responses and the sensorimotor cortex is made hyperexcitable. Somewhat similar studies have been conducted in rats on the organophosphate and carbamate insecticides, beginning with effects in utero. Pups born to parathion-treated dams exhibited delayed development of the startle reflex, eye opening, and the righting reflex. These and other experiments in mice show clearly that behavior is indeed affected by insecticides at doses which do not cause other symptoms of poisoning.

Lead. Several studies of CNS effects induced by heavy metals have provided additional insight into acute and chronic disorders. The studies show that there is a slowing of conduction velocity at high blood lead levels in children and that the effect has continued in known cases of plumbism for as many as two to twenty-five years after poisoning. Some of the neural manifestations of lead toxicity can be explained by effects on the synapse. However, these effects do not appear to account for the long-term neural and behavioral effects of lead, because they are usually reversible.

Long-term effects would appear to be more closely related to pathological changes at cellular and subcellular levels. After a convulsive dose of lead administered to experimental animals, there are significant alterations in components of pyramidal and astroglial cells in the brain. These changes can be seen before the onset of convulsions. Degenerative changes generally include cellular sclerosis or hydrops, each specific to certain cell layers of selected areas of the brain. Ultrastructural alterations in cells undergoing hydropic degeneration exhibit folding of the nuclear membrane, swelling and severe lesions of mitochondria, hypertrophy of the Golgi complexes and patchy chromatolysis of the Nissl substance (ergastoplasm). Progressive hypertrophy of Golgi saccules and vacuolization of ergastoplasm areas lead to degeneration of affected nerve cells.

Recent studies on neural effects have focused also on combinations of neurotoxins. Although no synergistic interaction between lead and organochlorines was noted in the case of epileptiform seizures induced by lead, concomitant exposure resulted in an increase in muscular incoordination characteristic of pesticide effects. Moreover, while lead exhibits only slight effects on motor performance, which is strongly affected by the pesticides, lead potentiated this effect when given in combination with DDT, dieldrin or lindane. Even nontoxic doses of DDT or dieldrin were made quite toxic upon administration of lead.

In addition to the well-documented role of lead and mercury in behavioral and CNS aberrations, evidence has been obtained that these substances affect auditory and vestibular processes. In chronic effect studies on the squirrel monkey, it has been shown that there is a reduction in the amplitude of evoked responses in auditory nerves as lead poisoning progresses. In general, no auditory or vestibular changes are seen during the first month of treatment but appear in increasing magnitude at two to three months.

Renal Disorders

Heavy Metals. Recent studies on organomercurials have resulted in identification of the functional lesion responsible for aminoaciduria in lead-induced kidney damage. The lesion occurs in the lumen of the tubules where the carrier system responsible for reabsorption of amino acids is located. Much the same kinds of lesions are produced by cadmium. A second locus of action of cadmium was identified as the peritubular cell membranes. Here at least four separate carrier systems actively transport different amino acids, and cadmium rapidly and specifically depresses uptake of dicarboxylic compounds but has no effect on that of other classes of amino acids.

Pulmonary Disorders

Coal Dust. Extensive studies on the pulmonary effects of coal dust and the role of specific components of the dust in the etiology and pathogenesis of pneumoconiosis are being conducted. It has been shown that there are quantitative differences in chemicals extractable from bituminous coal from mines in Pennsylvania and Utah. The most striking chemical differences are in nickel and iron contents, with the Pennsylvania coal being substantially higher in both. Correlates between the incidence of pneumoconiosis in miners in Pennsylvania and Utah show that the former is significantly higher, which is in accord with the high nickel and iron contents of the coal. Although these studies must be viewed as only suggestive, other data in the literature on nickel indicate that this metal is a potent sensitizing agent when inhaled. Therefore it appears to warrant more intensive study,

More fundamental studies were carried out also on the effects of coal dust *in vivo* on macrophages in rats. There is a substantial increase in the number of macrophages during the first month of exposure to the dust. However, phagocytic capacity, bacterial phagocytosis in particular, is substantially reduced. After three weeks of exposure, the animals showed extensive pulmonary disease, including pneumonia and pulmonary abscesses. The same kinds of syndromes were apparent in animals exposed to nickel oxide dusts. Other heavy metal dusts, notably those of cadmium, induced interstitial fibrosis with concomitant thickening of alveolar walls and subpleural connective tissues.

A series of studies conducted by grantees are concerned with effects of iron oxides, coal dust, barium sulfate, glass fibers, chrysotile and crocidolite on alveolar macrophages of rats and hamsters. Some species were exposed also to fly ash, cigarette smoke, carbon particles, and triphenyl phosphate. An increase was found in the number of cells obtainable by lavage upon administration of coal dust, chrysotile or iron oxide. The increase was largely attributable to the release of preexisting cells from a macrophage pool rather than to proliferation of new alveolar cells, since the incidence was seen only four hours after treatment--a period too short for appreciable cellular proliferation. Experimental confirmation of this was obtained by whole body irradiation (with X-rays sufficient to block mitosis) followed by administration of carbon particles.

Subsequent studies with iron oxide and other particles indicate that while the numbers of cells increase upon exposure, the phagocytic capacity of the cells is reduced and the bactericidal capacity of the lung is seriously impaired. This is in accord with the findings of other scientists in their work with coal dust.

Ozone. Further insight into the pulmonary damage and pathogenesis associated with exposure to ozone has been provided by grantees. Enzymes capable of breaking down lung tissue were found to increase in concentration in the lungs of rats exposed to 0.8 ppm ozone for five to seven days. Special biochemical tests have shown that lipid peroxidation resulting in damage to cell membranes is probably a basic mechanism of lesion induction. However, a protective enzyme mechanism was discovered whereby peroxides formed upon lipid peroxidation are detoxified via the glutathione peroxidase system. Some of the enzymes involved in this system were shown to be induced by as little as a seven day exposure to 0.2 ppm ozone. Thus, the pulmonary response is extremely sensitive and may be important as an adaptive biochemical change.

Similar studies by other investigators have provided further information relating ozone and NO_2 exposure to the development of emphysema and chronic obstructive lung disease. Rats exposed intermittently for a lifetime (about 2 1/2 years) to about 15 ppm NO_2 developed emphysema, a chronic obstructive lung disease (COLD), and exhibited an attendant loss of oxygen-absorbing surface area in the lung which resulted from loss of about two-thirds of the air sacs (alveoli). The main impact of injury initially was in the smaller airways that conduct gases immediately to and from the alveoli. These features resemble those in man and constitute a reasonable facsimile of human emphysema.

Ozone has proven to be approximately twenty times more injurious than NO_2 to the lungs of rats. It induced a similar type of disease but with certain significant differences. These are, mainly, a slightly deeper (more distal) position in the lungs of the initial injury and an early stimulation of connective tissue growth at the sites of injury. Considerable reaction becomes apparent within a few hours of exposure to less than 0.5 ppm--a concentration readily achieved at peak traffic hours in some urban areas. Cellular changes are obvious within four hours of exposure to about 0.9 ppm O_3, a level occasionally reached in heavy smog.

A mixture of O_3 and NO_2 at concentrations as low as 0.25 ppm and 2.5 ppm, respectively, caused definitive injury to the lining cells of the small airways in the lungs within 24 hours; and a mixutre of each at the occasionally high ambient level of about 0.1 ppm induced an advanced, lethal degree of emphysema within two months of continuous exposure.

When the airways and air sacs were naturally exposed to as little as 2 ppm NO_2 during respiration, the usual rate of replacement of the epithelial cells was found to be accelerated. Beginning about two hours after exposure to either NO_2 or O_3, ciliated cells of the small airways and of the thin, flat Type 1 cells from the adjoining alveolar walls begin to be sloughed, but are rapidly replaced by new cells. The new cells that appear are relatively resistant to the same concentrations of gases. This apparently constitutes an important adaptive and protective mechanism.

Lung Carcinogenesis

Studies conducted by a number of grantees have made it increasingly evident that induction of human lung cancer is multifactorial in nature and dependent upon long-term exposure to combined agents. Animal models have been developed which duplicate human bronchogenic carcinoma, and studies with these have shown for the first time that there is potentiation between benzpyrene and sulfur dioxide in tumor-induction. This has a significant bearing on the recent decision to relax controls on the use of coal and other high sulfur fuels during the energy shortage.

Studies on pulmonary effects of fiberglass plant dusts and polyurethane foam dusts revealed a number of associated changes in the lungs. With polyurethane foam dusts, both centrilobular emphasema and squamous cell carcinoma were seen. Other pathological changes included marked changes in capallaries, alveolar epitheleal cells and increases in the number and activity of macrophages.

Carcinogenic and Other Effects of Environmental Radiation

New techniques and information relating to the biological effects of sunlight and other sources of radiation have been developed by grantees. There has been a reawakening of interest in the biological effects of light, due in part to a real concern about possible alterations of the earth's atmosphere with the resultant changes in the quality of light from the sun, and in part to the proliferation and recognition of the plethora of photoactive chemical agents to which man is being exposed. Furthermore, the development of new, intense light sources for illumination has raised questions regarding the effects of chronic exposure to spectra differing greatly from those found in nature. Finally, the possible usefulness of light for therapeutic purposes is being seriously reconsidered.

The widespread use of phototherapy for hyperbilirubinemia in infants poses both great hope and possible serious side effects. The development of new, spectrally narrow, highly active lamps has reduced treatment time and increased speed of bilirubin destruction. However, serious side effects are possible, particularly on unprotected retinas in the presence of oxygen and on entrainment of biological rhythms. These, and other unwanted effects such as reduction in riboflavin and glucose-6-DP in serum, are being studied.

Development of new light sources has improved test systems for possible phototoxicity and photoallergenicity of a variety of environmental agents, and prediction of effects in man is now possible. Skin cancer can now be induced reliably in animals using the new equipment, techniques and animal models. This facilitates studies of the probable effect of alteration of atmospheric ozone, and interaction of light and chemicals in photocarcinogenesis. These new techniques, for the first time, make possible reliable investigations into the mechanisms and causes of cancers of the skin.

Mutagenesis and Reproductive Toxicology

The overall goal of this program is to safeguard the genetic heritage, the capacity to reproduce, and the health and well-being of the progeny of mankind against toxic agents of environmental origin. Immediate objectives are (1) to clarify the nature and structure-activity relations of chemicals in air, water, food, and occupational environments capable of altering the genetic makeup of man, reducing reproductive capability, or damaging the embryo or fetus at any stage of differentiation and development; (2) to develop reliable test systems with unequivocal quantitative relevance to man for detection and quantification of mutations in somatic and germinal cells and of teratological defects in the conceptus and fetus; (3) to elucidate molecular and cellular mechanisms in mutagenesis and reproductive anomalies; and (4) to provide overall intellectual resources for national programs in preventive and corrective medicine.

The frequency of major chromosomal abnormalities in man is currently about one in two hundred in Western society. Best estimates for the overall frequency of inborn errors is about twice that of visible chromosome disorders, i.e., in the range of one to two percent. These values include the many abnormalities of carbohydrate, lipid, purine, pyrimidine, and amino acid metabolism and aberrations in hemoglobin and serum proteins. They do not include the more subtle, ill-defined variations in intelligence, behavior, learning, aging, and disease susceptibility, at least some of which appear to be due to genetic anomalies or fetal damage. Presumably, the genetic burden has accumulated throughout the time span of human evolution, but no one can be sure whether individual aberrations accumulated at a steady baseline rate or at variable rates in response to environmental conditions. However, if the view is correct that mutation frequency is proportional, without the usual toxicological threshold exemption, to the sum of mutagenic factors to which man is exposed, the mutation rate today should be at its highest level in human history, for the environment abounds as never before in chemical and physical factors capable of causing genetic damage.

It has been observed that mutagenic agents frequently produce cancer and birth defects. Conversely, certain carcinogens were shown to be mutagenic. This dual effect is particularly notable in the case of alkylating agents, such as aziridines, nitrogen, sulfur and oxygen mustards, nitrosamines, epoxides, lactones, dialkyl sulfates, alkane sulfonic esters and many others.

In contrast to the inferential nature of mutagenesis hazards and interrelationships between mutagenicity and carcinogenicity, the teratological and reproductive effects of certain environmental agents are well documented. Familiar examples are the devastating effects of mercury on inhabitants of the Minamata Bay area in Japan during the 1950's and the malformed babies born to mothers who took thalidomide as a tranquilizer during the early 1960's. The Minamata tragedy resulted from contamination of the Bay area by industrial effluents of mercury used as industrial catalysts and by runoff of phenylmercury pesticides used in upland rice fields. Subsequently, a number of bays, lakes and streams in the United States, and in other countries (Sweden, etc.) were found to be similarly contaminated, primarily from mercury electrodes of chloralkali plants and from the use of mercurials as antifouling agents in paper pulp and other industries. Though measures have been taken to eliminate the sources of pollution, mercury is still present in significant quantities in some areas and is expected to recycle through food chains for many years.

Mutagenesis Test Systems. The available test systems involving microorganisms, cultured mammalian cells, insects and lower animals are being used as initial indicators of mutagenic potential. While such systems are not necessarily representative of man, they are useful in first tier screening to reveal mutagenic potential of test compounds. As better and more relevant systems are developed, refinements in interpretation of results in terms of human hazards will be possible.

Efforts by NIEHS scientists to develop better test systems involve several models. Seven different mutations of Neurospora are being studied which affect the sensitivity of the mold to radiation. Both quantitative and qualitative effects have been found and two of the strains, which sensitize the genome after ultraviolet and gamma radiation, are being studied with regard to sensitivity induction by chemical agents.

A major problem in meaningful mutagenicity testing is that of placing chemical mutagenesis on a quantitative basis in a eukaryote which can be reliably and economically analyzed. This is being attempted by using combinations of tritium-labeled ethylmethanesulfonate and ^{14}carbon-labeled DNA in sperm cells of the fruit fly Drosophila. With this technique it has been possible to increase several fold the sensitivity of methodology for quantitating alkylation at the seven position of guanine, which is a measure of mutagenic potential of alkylating agents. Since determinations are made directly on DNA, the method eliminates from consideration factors such as penetration into the germ line or metabolism of the chemical. By making comparisons between various species based on dose given versus dose measured as alkylations per nucleotide of DNA in the gamete, it is possible to factor out differences in metabolism and other events among species. The ultimate goal is to calibrate the method, using the economical Drosophila test system, with the more expensive mammalian test systems and to develop a reliable basis for extrapolating results to man.

The Institute is also fostering new initiatives to develop methods for testing and quantitatively evaluating a wide range of environmental agents in higher animals and humans and in their progeny. The intended applications of the tests are (1) to move from the simple indicator systems to tests that will establish the mutagenic potential of specific agents in man per se or proven models and (2) to determine the relative frequency of transmissible mutations induced by compounds or physical factors which act by different mechanisms and exhibit differential action on the various types of somatic and stem cells. Though somatic mutations are important and are obviously useful in assessing environmental hazards, it is the transmissible changes that are of primary long-range concern.

Methods are being developed for the electrophoretic analysis of serum proteins and various enzymes. Two strains of mice which show differences in electrophoretic patterns for specific enzymes are being irradiated and the offspring tested for specific changes. Previous mammalian systems for detecting point mutations, which result in changes in specific proteins, have been limited to a small number of genes which have visible manifestations. Enzyme screening in the system now being tested is limited only by the number of specific staining or other assay procedures available. Therefore, it is anticipated that it may be possible to test as many as 75 to 100 genes in a single individual.

Tests directly applicable to man are also planned for population and prospective epidemiological studies. By necessity such tests are limited to readily available fluid and cellular fractions of biopsy and surgical specimens, umbilical cord blood, amnionic fluid, lung and body cavity lavages, semen, blood, lymph, and urine. Efforts are being made toward further development and refinement of primary mammalian cell culture techniques and systems in which mutant (transformed) cells from the human cellular samples indicated can be distinguished and quantified.

Repair Mechanisms. Basic studies on the effects of environmental agents on DNA and repair mechanisms are proceeding along several lines. Mutant diploid cells have been isolated which are variant either with respect to X-ray survival characteristics or DNA repair capacity. DNA repair is measured by observing the rejoining of radiation-induced DNA strand breaks by use of alkaline sucrose gradient techniques. Two types of DNA damage and repair have been demonstrated: (1) an incisional process which probably represents the enzymatic recognition by the cell of radiation-induced base damage and (2) the direct induction of DNA strand breaks due to rupture at the phosphodiester bonds. Currently, cells are being isolated which are variant in both of these types of repair.

Primary skin fibroblasts have been cultured from patients who exhibited unusually severe skin reaction during radiaiton therapy. The cells show increased radiosensitivity in vitro as compared to skin fibroblasts derived from normal individuals. A defective step in the DNA repair process has been demonstrated in these cells, which apparently is the first instance whereby correlation between in vivo and in vitro X-ray sensitivity with a specific molecular process has been successful. Clinical radiosensitivity and/or chemical sensitivity, therefore, may be useful in devising new systems for the study of DNA repair mechanisms and the influence of mutagens on these systems.

Ongoing research has opened new horizons in several other areas which will provide a base for new methodology development. A grantee has been able to synthesize one turn of the helix of the DNA double strand. This can now be used as a target in testing for interactions between DNA and suspected carcinogens and mutagens. Because of its simplicity, the DNA fragment, containing all of the different kinds of building units of the whole DNA molecule, can be analyzed by available instruments (NMR). Thus the site of reaction and the influence of different foreign agents on other atoms of the double helix can be seen.

Such techniques hold great promise also for elucidation of basic processes and causal relationships in mutations that may be associated with aging and degenerative diseases. Cell lines have been cultured from progeria patients (the Hutchinson-Gilford syndrome), who are characterized by premature aging. The cells have been found to be deficient in DNA repair systems. Ongoing studies on the nature, causes and consequences of these deficits are expected to provide critical insight into the aging process per se, the propensity of older cells to mutate and to become transformed into cancer cells, and the possible role and mechanism of environmental factors in acceleration of mutations related to aging.

Mutagenic Agents

Recent studies have revealed several mutagenic agents which illustrate the concerns of NIEHS in this area. The drug hycanthone has been used by the World Health Organization to treat approximately 500,000 people for schistosomiasis. It proved to be extremely effective for this purpose; however, it was found to be a potent mutagen in a number of test systems, including mammalian cells in culture. The mutagenic properties of AF-2 (trans-2-[2-furyl]-3-[5-nitro-2-furyl] acrylamide), a food preservative used in Japan since 1965, were discovered recently quite by accident. This compound breaks chromosomes and causes gene mutations. It is structurally similar to other nitrofurans that have been shown to be carcinogenic, and to a number of derivatives marketed in this country for control of certain intestinal and kidney infections. Other studies have implicated PCBs (particularly Aroclor 1254) as chromosome breaking agents. On continuous feeding, the compound induced heavy chromosomal breakage during the second generation in the dove, which usually resulted in embryonic death. These findings indicate the importance of adequate test systems and of multi-generation testing at low levels of compounds in order to simulate the long-term human experience and to afford the kind of protection required to insure fidelity of the human genome.

Reproductive Toxicology

The work in reproductive toxicology involves basically the same approaches as that in mutagenesis, e.g., identification of teratogens, development of test systems and basic studies on molecular and cellular mechanisms of teratogenesis. Fortunately, few incidences of teratogenesis of the scope of those mentioned for mercury and thalidomide have been experienced in human populations. Nonetheless, efforts are continuing toward evaluation of environmental agents as teratogens to develop a fund of knowledge that can be used for appropriate regulatory activities by other agencies.

Metals. Various metals, including cadmium, indium, arsenic, cobalt, zinc, lead and mercury have been found to produce malformations in embryos. However, it has been shown that deficiency of zinc and manganese during pregnancy can also cause deformed offspring. Congenital defects caused by thalidomide and salicylates apparently are due to metal deficiencies induced by these compounds. Pregnant rats kept on a diet which was marginal with respect to zinc and fed thalidomide on days 8, 9 and 10 of the pregnancy had pups with a 20 percent incidence of skeletal and soft tissue malformations and a fetal resorption rate of 25 percent. Addition of zinc to the diet prevented the effect. Similar effects were shown upon treatment with salicylic acid.

The problem of congenital defects associated with methylmercury intoxication, as well as other aspects of the hazard of mercurials, is also being studied. The stage during pregnancy when the fetus is at greatest risk is of specific concern. Preliminary experiments indicate that low levels of methylmercury fed on day five or fifteen of gestation had no effect on the fetus. However, when given on day ten, a number of abnormalities appeared, such as hemorrhage in various areas of the fetus, including the brain and hind legs, and brains without a definite structure. These findings suggest that there is indeed a rather specific period during development when the fetus is most susceptible to mercury.

The biological enigma of copper in embryogenesis is being investigated also in the same laboratory. On the one hand, there is evidence that copper deficiency is detrimental to embryonic survival in the rat and chicken. On the other, there is evidence that an excess of copper has a detrimental effect on implantation and blastocyst development. Malformations of the heart appeared to be a specific result of copper toxicity, with the chelated form (copper citrate) being more embryopathic than copper sulfate.

A new aspect of lead intoxification pertinent particularly to children comes from the work of grantees, who have found a close relationship between nutrition, behavior, and lead toxicity. Calcium, iron, and certain other mineral deficiencies increase the toxicity by a factor of 20. Further, it was shown that growth and maturation of the nervous system is significantly retarded, owing to a slower rate of myelination of certain nerve fibers. These effects parallel those seen in chronic plumbism in children and suggest that a combination of malnutrition and lead intake will enhance the mental retardation associated with chronic lead poisoning. In behavioral tests, it was found that reduction in performance of rats parallels the retardation of myelination in the nervous system. These studies contribute in an important way to identification of basic effects of environmental lead of individuals in the general population who are most likely to be at greatest risk at a given lead level.

Basic studies may help explain the marked difference in toxicity of lead and mercury in the adult and young. It was found that when lead was administered to pregnant rats, the offspring developed tremors 25 days after birth. Mitochondria and other indicators of metabolism showed no effect. However, norepinephrine (NE), a hormone which affects muscle and heart action through the sympathetic nervous system, in the brain of pups from the treated mother was double that of normal pups. At 35 days, the NE level returned to normal in those animals that survived. The reversal of toxicity and nervous symptoms corresponds to the formation of the blood brain barrier in the rat at about 30 days after birth. This suggests that the absence of the barrier, or incomplete development, accounts for the high susceptibility of the very young rat to lead and to the hormone NE.

Subtle deviations in behavior, which might be helpful in diagnosis of early and marginal effects of toxic agents, are being studied in a number of laboratories. Grantees recently found that offspring of mice exposed to methylmercury on day seven or nine of pregnancy showed no signs of overt toxicity or of brain damage. However, they were able to demonstrate subtle behavioral effects. Pups from treated mothers were slow to begin exploration in an "open field" exploration test, showed a highly unusual backing phenomenon, and exhibited neuromuscular impairment while swimming. These findings suggest that tolerance levels of neuroactive environmental agents may have to be set on the basis of behavioral and/or learning criteria.

Pesticides. Since the finding of birth defects associated with use of the herbicide 2,4,5-T and the contaminant dioxin, a great deal of interest has centered around possible teratogenic effects of pesticides. Parathion, heptachlor, chlordane, and DDT have been investigated for fetocidal effects. Parathion, when fed to the mother at very low doses, was found to be highly toxic to the fetus. Resorptions were most numerous during the latter part of gestation, the period of maximum organ development and maturation. These findings are particularly significant because of the large-scale use of parathion as a substitute for the persistent chlorinated hydrocarbon insecticides. It is also significant that the effects of parathion in the body are not limited to short-term effects on the nervous system as toxicologists once believed.

The perinatal effects of a number of pesticides have been examined. Embryotoxicity and teratogenicity have been demonstrated for many compounds, including bidrin, paraquat, dinoseb and 2,4-dinitrophenol.

Salicylates. Aspirin and other salicylates have been recognized as teratogens in rats for many years, but until now little was known about their mode of action. Ongoing studies clearly implicate dietary factors and perhaps inherent factors in the mother related to essential metal metabolism as an important aspect of birth defects. They strongly suggest that prolonged intake of drugs or environmental agents that strongly bind essential metals during pregnancy increases the probability of defective offspring.

A considerable effort has been devoted by intramural scientists toward the development of new teratological test systems. While it is too early to predict the success of such techniques, they illustrate new thinking and new directions being applied toward development of reliable test systems.

Techniques have been developed for the culture of fertilized eggs and embryos from several animal species. During this period of living outside the mother's body, the embryo can be exposed to known chemicals, in precisely known amounts, for exact periods of time, and at selected stages of development. The eggs and embryos thus treated in culture can be transferred back into the mother and allowed to mature for varying periods or even be born before further examination for defects.

It is also practical to expose only certain parts of the fertilized egg to suspected toxins and teratogens. Using micromanipultators, the chemicals are injected into only certain cells of the embryo or selected areas of a single cell. One or more cells so treated can also be transferred to, and incorporated in, a recipient embryo. Parts of a treated cell, such as a nucleus, can be transferred to an untreated cell or group of cells. Such studies help localize even more precisely the critical cells of an embryo, or the most sensitive part of the critical cell, that is affected by toxicants. Such techniques of cell culture and microsurgery have not been applied previously to a study of birth defects produced by drugs, but they appear to hold great promise for future studies in teratology.

NATIONAL EYE INSTITUTE

NATIONAL EYE INSTITUTE

Mission and Program Mechanisms

The mission of the National Eye Institute is to support and conduct research and research training related to disorders of the visual system. The objective of this research is to increase the knowledge available to prevent, diagnose, and treat these diseases and to foster improved rehabilitation of the blind and visually disabled.

The six years of NEI's existence have seen significant development of the Institute and its programs. When NEI was created in 1968, the budget for vision research within NIH was $20.7 million. The Fiscal Year 1974 appropriation level was roughly twice that amount, exceeding $41 million.

The Institute supports the broad field of vision research through five major programs: Retinal and Choroidal Diseases, Corneal Diseases, Cataract, Glaucoma, and Sensory-Motor Disorders, relying primarily on the research grant mechanism to achieve program objectives. However, research contracts are also used, and an active intramural program, including laboratory, clinical, and epidemiological research, makes its own unique contributions.

Program workshops have been held to assess the state of knowledge in specific areas related to vision research to help assure that Institute resources support the most promising aspects of research. Program workshops for the Glaucoma, Cataract, Cornea, and Retinal and Choroidal Diseases programs have identified gaps in knowledge which the Institute has in turn communicated to the research community at large. The coordination and cross-pollination of ideas that has resulted from these conferences has also been helpful to the Institute and to investigators in the field. These workshops will be reconvened periodically to assess new developments and recommend the revision of research goals when necessary.

The National Advisory Eye Council, which consists of non-Federal experts in the visual sciences and representatives of the public, advises the Director of the Eye Institute concerning the formulation of policies relative to the Institute's programs. To aid its fulfillment of this responsibility, the NAEC recently established a Vision Research Program Planning Committee. With the help of consultants who are experts in specific fields of vision research, this Committee will periodically report generally on the status of vision research in the United States, specifically on the scope of the National Eye Institute's support, and the major scientific needs and opportunities in and among each of the Institute's five research programs. This information and an analysis of possible methods for relating resources to research opportunities form the basis for the recommendations of the Committee to the Director of the Institute on program priorities and program balance.

As noted earlier, the research grant is the primary mechanism used by the Institute for supporting research in the basic biological sciences relative to vision and the application of such knowledge to the improved prevention, diagnosis, and treatment of visual disorders. The research grant enables the investigator to formulate the precise scientific questions to be answered. No specific service is expected to be furnished nor is adherence to detailed specifications of performance required. Freedom of approach is reserved for the recipient of the award. The research grant is particularly appropriate for the Eye Institute's program because it is best suited for the support of basic research. Such fundamental knowledge is needed to solve many of the major problems which presently exist in each of the major program areas, particularly in Retinal and Choroidal Diseases and Sensory-Motor Disorders.

The contract, on the other hand, is used by the Eye Institute when a specific service or end product is needed. For example, rats with retinal degeneration have been bred under contract to NEI and made available for research to the scientific community, and a multi-institutional clinical trial is being performed under several contracts to evaluate the effect of photocoagulation upon diabetic retinopathy.

Program

Retinal and Choroidal Diseases

Diseases affecting the retina and the vascular tissue underlying it, the choroid, account for more blindness and visual disability than any other group of eye disorders. Degeneration of the macula, that part of the retina responsible for central vision, is the most common untreatable eye condition among the elderly and is a leading cause of blindness in this group. Disability from retinal disease associated with long-standing diabetes is now one of the leading concomitants of this disorder and a major cause of new adult blindness in the United States. At least 76,500 people in this country are "legally" blind from retinal diseases and thousands more, though technically not blind, are so severely disabled they cannot read ordinary newsprint, even with glasses. For most retinal diseases there is no means of prevention and little chance of cure. In a recent survey of practicing ophthalmologists, conducted by Research to Prevent Blindness, Incorporated, retinal diseases were rated as those most difficult to treat and most in need of basic and clinical research.

Progress against retinal disorders has been blocked by a lack of fundamental knowledge concerning the structure and functioning of this highly complex tissue. Study of the retina has been particularly impeded by lack of animal models of human retinal disease and of objective means for the differential diagnosis of retinal disorders.

Important studies underway in this area include projects aimed at understanding how the choroid nourishes the retina, clarifying the detrimental effect of light in certain circumstances on retinal structures, increasing the resolution attainable in photographing the retinal vessels with the aid of fluorescent dyes, developing new techniques for measuring blood flow through the retina and choroid, and learning the underlying cause of such inherited retinal disorders as retinitis pigmentosa.

Major areas in need of further research include study of the pigment epithelium, a thin layer between the neural retina and the choroid which is believed to be the primary site of many retinal degenerative diseases. Determination of factors affecting the adhesion of the retina to the pigment epithelium could lead to more effective treatment or even prevention of retinal detachment. Research on the electrical functioning of the pigment epithelium and the effect of chemicals and drugs on this activity is essential for the development of improved methods of diagnosing retinal disease. Better understanding of the relationship between the various types and layers of retinal cells would shed light on why only certain areas of the retina are affected in various degenerative diseases. New and improved optical methods for examination of the back of the eye are needed.

In general, the field of retinal research requires a multidisciplinary approach with laboratory scientists in such fields as biochemistry, physiology, and anatomy working closely with clinicians to solve the many problems related to disease of this tissue.

Corneal Disease

Though not a leading cause of blindness, diseases of the cornea rank high as a source of visual disability and are the most painful disorders affecting the eye. The cornea is also that part of the eye most susceptible to injury, an occurrence which accounts for a large proportion of accidents on the job, at school, in the home, and in leisure activities. The cornea is one of the major components of the eye's focusing system, and irregular curvature of the cornea, astigmatism, is a common cause of refractive error.

Diseases affecting the cornea are those caused by infectious agents including bacteria and viruses, congenital and developmental influences, and degenerative processes. Such disorders may be treated by drugs, transplantation and other surgical procedures, soft contact lenses, and, most recently, by the controlled application of heat.

Areas of research currently emphasized are studies of immunologic mechanisms in corneal disease, herpes simplex virus infections, corneal opacification, edema, drugs, and means of delivering them. Other important areas of corneal research include the epidemiology of corneal disease, relationship of inflammation to tissue destruction, studies of the corneal tear film, transplantation and artificial corneal implants, physical factors in corneal disease, nonspecific inflammation, and tumor virology and immunology.

Specific areas of corneal research being emphasized include studies of (1) the immune mechanisms of the cells of the cornea, including the possible role of autoimmunity in certain corneal diseases, (2) recurrent and deep herpes simplex infections, including the effective use of antiviral drugs, human interferon, and steroids for active and preventive therapy, (3) the process by which the normally transparent structure of the cornea develops and is maintained in order to better understand the formation of scars in the cornea and the possible transformation of such damaged tissue back to normal, (4) the system of pumps and barriers that contributes to the normal water balance and cohesion of the cornea which when interrupted by disease or injury causes edema or swelling of the tissue, and (5) development and testing of new vehicles and devices, such as drug-impregnated plastics, for the continuous delivery of medication to the cornea, for both convenience to the patient and reducing the number of applications needed to obtain the desired effect.

Cataract

Despite the availability of surgery to remove cataracts and subsequent restoration of normal visual acuity in approximately 95 percent of cases, this eye condition remains one of the leading causes of blindness in the United States and throughout the world. Many people fear cataract surgery; others lack the financial resources, or have other reasons for not having cataracts removed. A survey by Research to Prevent Blindness, Inc., of ophthalmologists showed that cataract was the disease most frequently encountered in their practice. Even though approximately 400,000 cataract operations are performed annually (at a cost of approximately $480 million) an estimated 3 million people in this country have some degree of opacity in the lens of one or both eyes. Non-surgical treatment of cataract would therefore be a highly desirable accomplishment. Prevention of this disorder is the ultimate objective of cataract research.

Investigators working in cataract research now believe that a solution to the cataract problem is feasible. One reason for their optimism is that there are now a number of ways to induce the formation of cataracts in animals, although no suitable models for senile human cataract, the most common cause, are currently available. Secondly, the lens can be cultured and maintained in the test tube for relatively long periods of time; in fact, a number of physiological changes characteristic of cataract can be duplicated in the laboratory. Thus, despite the relatively small number of investigators in the field, some hopeful leads have been uncovered, including (1) the prevention, through chemical means, of experimental sugar cataracts in animals, such as those which may occur in humans with diabetes or galactosemia, (2) the finding that in both animal and human lenses certain proteins clump together with aging and are able to scatter light and thus cause cataract, (3) the finding that certain kinds of experimental cataracts in animals are reversible, (4) the discovery of new cataract-inducing drugs which could increase the scope of animal models of the disease, and (5) the recognition of the possible importance of combinations of factors acting together to produce human cataract.

Such progress has pointed the way to further research in this field. Specific opportunities and needs include (1) cataloging the development of cataract and differentiating the different types of cataract which occur in humans and animals, (2) detailed study of the biochemistry and physiology of the normal human lens, (3) additional investigation of the aggregation of lens proteins and how this mechanism relates to cataract formation, (4) more detailed studies of the interaction of the various lens proteins with each other, (5) studies of drug-induced cataracts, (6) continued investigation of the normal development of the lens and how it maintains its normal transparency, (7) systematic searching for unreported or unidentified sources of cataract, particularly in patients with known inborn errors of metabolism, and (8) further development of animal models for cataract, particularly for human senile cataract.

Glaucoma

Glaucoma is the name of a group of diseases characterized by loss of visual function associated with increased pressure within the eye. It has been estimated that nearly 800,000 people in the United States have glaucoma. For those with chronic glaucoma who were fortunate enough to have their condition diagnosed before serious visual loss occurred, regular administration of expensive, and frequently uncomfortable, medication is necessary to keep the disease in check and preserve remaining vision. For those who cannot be helped by medication, surgery is often the last resort. Despite continued widespread community and industrial screening programs, glaucoma remains a leading cause of blindness and visual disability. More than 34,000 Americans are blind from this disease.

Progress against chronic glaucoma, the most common form, has been impeded by the lack of reliable and simple methods for early diagnosis, the variability in efficacy and undesirable side effects of current glaucoma drugs, the limited effectiveness and high risk of complications from surgery used in cases of uncontrolled chronic glaucoma, and the lack of means of reversing even early losses of visual field.

Glaucoma research is focused on developing better means of early detection and diagnosis including (1) classification of the elevation in intraocular pressure in response to steroid drugs which occurs in otherwise healthy individuals, a phenomenon which may lead to a test for glaucoma susceptibility, (2) photographs of unique markings on the retina of glaucoma patients which may make possible quick and relatively easy determinations of the presence and extent of visual loss in glaucoma,

(3) relating an increase in the vertical dimension of the optic nerve head to identify the early presence of glaucoma, and (4) development of an animal model for chronic glaucoma.

A wide array of drugs is needed for treating glaucoma because no one medication is suitable for every patient. Physicians often must try a number of drops in different doses and on different schedules before an individual's glaucoma can be brought under control. The drugs now used are effective but have a number of disadvantages: some lack specificity and affect the nervous system generally, some are ineffective in treating certain individuals, some produce an allergic reaction after prolonged use, some have undesirable side effects, while others decay into toxic substances. New drugs, or improved versions of old ones, and better systems for administering drugs, are badly needed.

Surgery to open new outflow channels must be undertaken when medical treatment of chronic glaucoma is not effective in controlling pressure or preventing loss of vision. This "filtering" operation is often not successful and may result in serious complications. New ways must be found to improve the outcome of such surgery. New methods involving the use of cryosurgery (cold), lasers, and enzymes which could open up new outflow channels need to be developed and evaluated in experimental animals before being applied to humans.

The prospect of microsurgery for glaucoma is particularly exciting. Using an operating microscope and miniaturized instruments, it may be possible to eliminate the resistance to outflow in the microscopic outflow channels which drain the eye. If this could be accomplished routinely, physicians could be able to attain a degree of pressure control equal to or greater than that obtained with current methods with a reduced incidence of complications. The results of surgery may also help to localize the site of resistance to outflow and provide important information on the nature of glaucoma.

Sensory-Motor Disorders

This group of diseases constitutes 17 percent of all cases of blindness in the United States and includes the least understood of all causes of visual disability. Some sensory-motor disorders, such as strabismus, can be corrected in the young child, but not in older children and adults. Disorders of the optic nerve, ocular muscles, and visual centers of the brain fall in this category, and studies of the mechanisms underlying these conditions shed light not only on the functioning of the eye but of sensory systems in general, including the initial processing of sensory information, route and means of transmission of information to the brain; encoding, further processing, and decoding by brain centers; and feedback from the brain to the sense organ and other structures within the body.

Research in this program centers on the role of early visual deprivation in the causation of certain sensory-motor disorders; the development of better surgical methods for correcting disorders of the ocular muscles; and the organization and interrelationship among the various types of cells in the brain which subserve such functions as coordination of images from the two eyes, three-dimensional sensation, selective perception, and color vision.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Introduction

The National Institute of General Medical Sciences supports programs in research and training which undergird areas of research of all the other mission-oriented institutes, or are, in particular, multidisciplinary in character.

The broad definition of the fields of responsibility of NIGMS is based on Public Law 87-838, Sec. 442:

> An institute for the conduct and support of research and research training in the general or basic medical sciences and related natural and behavioral sciences which have significance for two or more institutes, or are outside the general area of responsibility of any other institute, established under or by this Act.

Definite salients may be discerned in this broad base of support. Through advice from consultants and by efforts of institute staff, areas of high scientific opportunity, potential or need are identified and receive special attention. Specific fields may also be defined by testimony at Congressional hearings and through request and/or approval by higher administrative echelons of the Executive Branch.

Program priority is based primarily on the opportunities for major advance in knowledge in a given program area and on the probability of contributing knowledge useful to the health of man. Resources are distributed on the basis of the value judgment of advisory groups and the National Advisory General Medical Sciences Council, and program emphasis as established by Congress and the Executive Branch.

Long-range planning is focused within the Office of the NIGMS Director, acting with advice of the NIGMS Council, and receives a variety of inputs from technical staff, and from consultants both formally appointed or retained on an ad hoc basis. Guidelines on more specific and technical aspects of support are often provided through institute workshops and conferences.

NIGMS, unlike the other NIH institutes, does not maintain an intramural program of laboratories or clinics. Rather, support for research and training takes the form of grants-in-aid to universities, medical schools, and similar institutions throughout the country. Contracts may be utilized to attain discrete objectives which the director and staff judge will accelerate progress in a priority area. These contracts support research and development activities in Government laboratories, in industrial organizations, or in nonprofit institutions.

Overview of Research Programs

The Institute's activities are divided into five programs:

1. Pharmacology-Toxicology
2. Biomedical Engineering
3. Clinical and Physiological Sciences
4. Genetics
5. Cellular and Molecular Basis of Disease

Pharmacology-Toxicology

The Pharmacology-Toxicology Program is a coordinated national program directed at improvement of medical therapy and of the safety and efficacy of therapeutic agents used in the delivery of health care through increased understanding of the mechanism of drug action and the effect of various factors on this action. Research supported by this program is providing a rational basis for the safer use of presently available drugs and is contributing to the design of more effective therapeutic agents.

A major thrust of this program has been in the special university-based centers which provide for an integrated continuity of effort on the part of both basic and clinical scientists. Investigations include drug design and the predictability of effects, drug metabolism and disposal, and the control of toxic effects.

Briefly, several research areas are described:

> Pharmacogenetics. Inherited variations in an individual's response to drugs require that different dosage regimens be developed and used. The toxicologic implications of inherited differences in the metabolism and deactivation of both drugs and environmental agents are receiving attention. Research in this area includes studies demonstrating wide variations in the therapeutic effectiveness, investigations to determine whether drugs have different reactions in different patients, and studies on inherited differences in the binding of drugs to blood proteins. Leads in this area have already provided evidence of public health relevance.
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> Perinatal Pharmacology. An understanding of the perinatal development of drug metabolizing enzyme systems is rapidly

emerging. Most drugs pass the placenta of the mother and may be found in the plasma and urine of the newborn. Basic differences between infant and adult response to drugs are being elucidated.

Immunopharmacology. Research on immunosuppressive drugs will be of importance in the control of organ rejection following transplantation, modification, and treatment of diseases with an immune component, such as arthritis, systemic lupus erythematosus, and other collagen and auto-immune diseases.

Biomedical Engineering

The biomedical engineer combines the mathematical skills and analytical ability of the engineer with the life scientist's understanding of biology to solve problems in research on living systems and the delivery of health care. Engineering methodology is also applied to the processing of medical information, such as for clinical evaluation and management of critically ill patients. This includes development of new systems for rapid data acquisition and display involving new types of transducers and integrated electronic circuitry, and development and application of mathematical models of physiological control systems to predict more accurately and rapidly the clinical status of the acutely ill patient. In selected instances, prototype instruments, devices, and systems are being developed that will be useful in the prevention, diagnosis, and treatment of medical disorders.

As medicine becomes less of an art and more of a science, whole new arrays of quantitative techniques and modes of analysis and treatment are required. Toward this end, biomedical engineering centers with broadly based capabilities offer excellent opportunities for the successful application of the concepts, methodologies, and techniques of engineering science to biomedicine.

NIGMS research and development in biomedical engineering presently supports projects in the areas of the application of communication and control theory to the study of biological systems, biomedical instrumentation, biomaterials, patient monitoring, and computers for biomedical research. In the coming years, research emphasis will be placed on (1) the use of the principles and practices of engineering science to explore life processes at the molecular level, (2) the application of engineering control theory for the study of physiological processes, (3) data processing for computerized techniques for clinical decision making, and (4) microelectronic instrumentation for physiological studies and patient care.

There are several related subunits in this program:

Automation of Clinical Laboratories

The objectives are to develop ways to mechanize and better automate the operations of the clinical laboratory and cope more adequately with the mounting workloads. At the same time, efforts are aimed at reducing unit costs per test. The program currently supports research and development of new and refined types of separation techniques, new modalities for the measurement of biological substances, more sensitive instruments, and computer hardware and software suitable for the automated analysis of biological specimens. Research emphasis in the coming years will be on (1) more accurate and direct methods for the determination of chemicals in blood; (2) more rapid and accurate methods for the assay of enzymes and hormones, (3) cytochemistry, cell preparation, and application of automated cytology techniques, (4) more rapid, economical, and specific viral diagnostic procedures, (5) the development of more mechanized and automated analytical instruments, and finally (6) positive specimen identification and automatic accessioning of biological samples from the patients.

Diagnostic Radiology

The objectives of this program are to develop and apply new knowledge and techniques for the improved diagnosis of disease by the use of radiation, radioisotopes, and ultrasound. It comprises a broad research effort utilizing ionizing radiation, radioactive isotopes, infrared radiation, thermography, and ultrasonic techniques for the investigation of structure and function in disease, and the development and evaluation of new diagnostic equipment.

An increasingly important area is diagnostic nuclear medicine, which offers unique opportunities for improved visualization studies of the dynamic function of organs and of regional blood flow (e.g., altered blood flow resulting from brain tumor). Extensive work currently is underway in the development of methods and instruments for image amplification and of techniques such as tomography, cine-radiography, and visualization of contrast media. Future plans include the support of research on the use of computers for automated storage and retrieval of radiologic images and ways of transferring and recording radiologic data. Efforts are also underway to partially automate the detection of radiologic abnormalities.

Clinical and Physiological Sciences

The goal of this program is to broaden and strengthen the scientific base of the several areas of clinical medicine for which the Institute has responsibility. Coordinated basic and clinical investigations relating to specific areas such as anesthesiology and trauma are intended to foster a more rapid application in clinical practice of new knowledge gained from research in such areas as cell biology, physiology, biochemistry. pharmacology, behavioral sciences, and bioengineering.

Anesthesiology

Research in the program is concerned with the mode of action of inhalation anesthetics and muscle relaxants, the nature and control of pain, basic physiologic and metabolic changes resulting from anesthesia, the management of respiratory failure, obstetrical and neonatal resuscitation, the handling of postoperative respiratory complications, and the pulmonary and systemic effects of drowning. Areas of future emphasis include:

- The development of means for instantaneous detection of hypoxia;
- The study of causes and prevention of post-anesthetic complications, such as liver necrosis, kidney failure, and respiratory failure;
- Improved detection and treatment of malignant hyperthermia;
- Identification of conditions which affect mortality following intracranial operations;
- Development of better treatment methods for localized cerebrovascular insufficiencies; and
- Study of both the physiologic and psychologic aspects of pain and the possible ways of treating it.

Trauma

The objectives of the trauma program are to discover better ways to prevent death from injury, mitigate pain, speed recovery of patients, and to lessen the degree of disability caused by injuries. Current research aims at the thorough understanding of the biochemical and physiological changes that occur in reaction to trauma, as well as the treatment of post-traumatic infections and the proper management of wound healing and rehabilitation. Areas of research being given increasing emphasis include:

- A study of the psychological responses to severe injury.
- Nutritional requirements of convalescing victims.
- Extensive programming of research on the special problem of burn treatment.

Behavioral Sciences and Adaptation

This area encompasses a broad range of research with emphasis, on the one hand, (1) to the application of behavioral science to psychological factors in health and disease, the interaction of the patient with his social environment, and an understanding of the doctor-patient relationship; and on the other hand, (2) to the interdisciplinary investigations relating behavioral science to genetics, physiology, and pharmacology.

Genetics

Directed toward gaining a better understanding of the processes and mechanisms of inheritance, the objectives of this program are the prevention, therapy, and control of genetic disease in man, including diseases directly resulting from genetic causes or multifactorial diseases with a strong hereditary component. While the various categorical institutes at the NIH appropriately consider the treatment of individual diseases with a genetic background, NIGMS treats the problem of human genetic disease as a generalized phenomenon involving common mechanisms, amenable to elucidation through broad fundamental research approaches.

Current research is concerned with improving the techniques for studying mammalian genetics, the technolgoy for cell and tissue culture, and the establishment of interaction between laboratory and clinical research in genetics. To develop further the latter, research center grants have been made to institutions where basic scientists and clinical scientists are encouraged to collaborate.

Special emphasis in the coming years will be placed on efforts to extend the genetic maps of human chromosomes, means of identifying carriers of genetic diseases, elucidating the control mechanisms of genetic expression in man, and the further development of a library of human cell lines, which will be used to seed stocks of well-characterized tissue cultures available to research workers in this field. A better understanding is sought of multifactorial genetic diseases, including hypertension, atherosclerosis, diabetes, and cancer. These diseases have strong genetic components, but unlike the simpler, single-gene diseases, they are probably due to the interaction of more than one gene and the environment. The program pays continuing attention to the possible implications of new research results for society and the ethics involved in medical practice. An assessment is being sought of the current state-of-the-art of genetic counseling, with the goal of possibly establishing guidelines for effective counseling.

Cellular and Molecular Basis of Disease

The objectives of this program are to gain a deeper understanding of the complex structure and function of human cells and their component parts. The research supported by this program includes a wide range of investigations: (1) on the physical, chemical, and biochemical description and analysis of the molecular events that occur within normal and diseased cells; (2) on the structure and function of the membrane system of cells and of subcellular organelles that have been shown to have vital roles in the cell; and (3) on the integration of these two approaches for focused studies on the pathology of the cell described in subcellular and molecular terms. Nearly all diseases can be viewed ultimately as the direct result of abnormal function of cells. Areas of research emphasis include (1) detailed submolecular structure and mechanism of action of protein enzymes and other biological molecules; (2) consolidation of knowledge of subcellular organelles and components into more precise concepts of how the cell functions as a unit; (3) cell/cell interaction during morphogenesis and day-to-day function as tissues and organs; (4) studies on the mechanisms by which enzymes bring about their catalytic effect--in particular the role of metal atoms as essential parts of some enzymes and studies on the reactivity of these metal ions and the implications for possible modification of this activity; (5) elucidation of the relationship between chemical structure and biological activity. Plans in the program include the establishment of additional molecular pathology centers, which seek to promote increased collaboration among pathologists and scientists from clinical departments with biochemists, biophysicists, electron microscopists and other basic scientists. These centers are expected to speed our understanding of the cellular and molecular basis of disease.

Research Training

In addition to support of research, the Institute has, in the past, supported an extensive program of training of scientists.

These programs were designed to meet national requirements for well-trained basic bioscience and clinical science manpower. This effort was also directed at meeting the demands of medical schools, teaching hospitals, and universities for faculty of the high competence required for effective teaching of increasing numbers of health professionals. Stress was placed on those disciplines and areas in which highly motivated research-trained manpower is in critically short supply.

Training programs supported by NIGMS enabled graduate schools and medical schools to strengthen and improve their research training capabilities by providing support for staff and for facilities and supplies. Newly emerging disciplines were encouraged, and interdisciplinary perspectives are emphasized. Some 20 basic science and clinical disciplines were represented within the purview of the Institute.

The research training program of the Institute is being restructured, as a result of new legislation, "The National Research Act." This Act provides for research training in the form of individual and institutional fellowship program in subject areas in which there is a need for personnel. The Institute expects to continue to play a large role in the support of predoctoral research training.

NATIONAL HEART AND LUNG INSTITUTE

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NATIONAL HEART AND LUNG INSTITUTE

Introduction

The National Heart and Lung Institute conducts and supports research on the structure and function of the heart, blood vessels, blood and lungs and on the prevention, diagnosis, and treatment of diseases that affect them.

Collectively, these diseases affect more than 30 million Americans and are the number one cause of death and disability in the nation. By far the most important cause of death plus three others among the ten leading causes of death in the United States fall within the scope of these problems. Heart and blood vessel diseases alone account for more than one million deaths each year. Approximately one quarter of these deaths occur in persons age 65 or less, the most productive years of a person's life. In close to 100,000 persons with heart and blood vessel disease, sudden unexpected death is the first and only evidence of heart disease. The number of days of bed disability in 1971 directly attributed to the above disease problems was approximately 210 million. The total economic drain on society due to problems related to these diseases has been estimated at more than $40 billion annually.

Recognition of the magnitude of these problems resulted in the enactment of the National Heart, Blood Vessel, Lung, and Blood Act of 1972. This Act provides a mandate for attacking the identified problems and requires the Director of the National Heart and Lung Institute (NHLI), with the advice of the National Heart and Lung Advisory Council, to develop a program for a national effort against these diseases.

The first five-year Plan for the National Heart, Blood Vessel, Lung, and Blood Program was completed in May 1973 for transmission to the President and Congress and the first annual report on the program was submitted in February, 1974. The NHLI has also been named to coordinate the accelerated program of research, treatment, and community services in sickle cell anemia, a crippling, often fatal disease that strikes black people primarily. This program in sickle cell disease is included within the total National Program.

The National Program Plan presents a broad program strategy for achieving improved health:

> ". . . to marshal national resources for promoting and restoring health, and for preventing and treating disease more effectively by:
>
> - Initiating an ordered sequence of coordinated program activities ranging from the acquisition of new knowledge to demonstration and control programs in the health care setting of the community
> - Providing adequate program evaluation before the application of existing knowledge to health care delivery systems
> - Evaluation of the impact of implemented programs on the health of the American people."

Within this strategy and in accordance with the National Heart, Blood Vessel, Lung, and Blood Act of 1972, a multifaceted National Program has taken shape. The scope of the evolving program ranges from molecular studies of single human cells to studies of the effects of pharmacological agents, to development and evaluation of new types of therapy involving advanced bioengineering concepts. It also includes studies of patient attitudes and motivation to adhere to prescribed therapy over long periods of time in spite of the absence of symptoms of disease; behavioral studies; and investigations dealing with man's ability to cope with underwater and space environments, reaching into future vistas of mankind.

The National Heart, Blood Vessel, Lung, and Blood Program gives special emphasis to prevention of heart attacks, the greatest killer in our nation; to education on high blood pressure, since millions of our citizens do not know that they have it and that it can be treated to expansion of the attack on lung diseases, a heretofore neglected area; and to the development of a national blood policy, a critical national need. The previous emphasis on the control of sickle cell disease is being continued.

The overall goals of the National Program are to: promote health, prevent disease, treat disease, and restore health. To advance towards these goals the Institute, through the National Heart, Blood Vessel, Lung, and Blood Program, is focusing primarily on three types of program efforts:

- Research
- Prevention, Control, and Education
- Manpower Development

The programs of research are fundamental to the National Program. Future developments in the prevention, treatment, and control of disease are dependent upon availability of basic knowledge of the life processes, how and why these change with disease, and how such changes might be controlled or reversed. Also, through research, the knowledge necessary for promoting and restoring health will be developed. The Institute supports a broad range of fundamental and clinical research in order to develop this essential information base for achieving the overall goals of the National Program. The prevention, control, and education programs deal with the application and dissemination of knowledge already developed and evaluated through research, but not yet effectively applied toward the prevention, control, and treatment of disease. These programs are an essential link between biomedical research and health care. Their purpose is not to deliver health services but rather to improve and expedite the transmission of fundamental research advances to the public and to medical practitioners and thereby help to promote the health of our citizens. The development and maintenance of highly skilled manpower at all levels are of critical importance in the planning and implementation of our national effort against heart, blood vessel, lung, and blood diseases.

An overview of program developments, of recent progress, and future challenges is presented below for each of heart and vascular diseases, lung diseases, and blood diseases, according to the current program structure of the National Plan as illustrated in Table 1.

Table 1

National Heart, Blood Vessel, Lung, and Blood Program Structure

Heart and Blood Vessel Diseases

1. Arteriosclerosis
2. Hypertension
3. Cerebrovascular Disease
4. Coronary Heart Disease
5. Peripheral Vascular Disease
6. Arrhythmias
7. Heart Failure and Shock
8. Congenital and Rheumatic Heart Disease
9. Cardiomyopathy and Infections of the Heart
10. Circulatory Assistance

Lung Diseases

1. Structure and Function of the Lung
2. Pediatric Pulmonary Diseases
3. Emphysema and Chronic Bronchitis
4. Fibrotic and Immunologic Lung Diseases
5. Respiratory Failure
6. Pulmonary Vascular Diseases
7. Inhalation Diseases
8. Respiratory Assistance

Blood Diseases and Blood Resources

1. Bleeding and Clotting Disorders
2. Sickle Cell Disease and Related Disorders of the Red Blood Cell
3. Biomaterials
4. Blood Resources

Heart and Blood Vessel Diseases

An impressive array of opportunities and needs can be pursued in the cardiovascular disease area at this time. The approaches that currently appear most promising and most needed to develop new knowledge about heart and blood vessel diseases are summarized here.

Cardiovascular disease is by far the number one health problem in the United States. In 1971, an estimated 1,022,000 Americans died from heart and blood vessel disease, i.e., more than 53 percent of deaths from all causes. Of these deaths, heart attack was responsible for 676,000, and stroke for 208,000. Currently, an estimated 28 million Americans have some major form of heart and blood vessel disease.

Arteriosclerosis

Arteriosclerosis is the most common serious disease affecting man in Western society. It is responsible for about 85 percent of the deaths from cardiovascular disease in the United States.

Recent research has developed a significant amount of new knowledge about the causes and development of arteriosclerosis. Significant positive statistical associations have been demonstrated between arteriosclerotic disease and hyperlipidemia, hypertension, heavy consumption of cigarettes, physical inactivity, personality type, and other factors. However, we do not yet completely understand the causal relationship of these variables to arteriosclerosis. Current studies on molecular and tissue interactions promise to help explain the development of arteriosclerosis and offer opportunities for its prevention.

Obviously, preventing the events leading to atherosclerotic plaque formation in the arteries would be better and far less costly than attempting to treat the resultant vascular disease and its sequelae. Thus, the overall goal of the Institute's programs in arteriosclerosis is to obtain a better understanding of its basic process and to improve the prevention, diagnosis, and treatment of the process and its sequelae.

Strong efforts to find solutions to the problem of arteriosclerosis are being made in fundamental research, nutritional studies, and clinical investigations. As a result of these efforts, the Institute can report significant progress in adding new knowledge. Examples of these advances are given below.

The processes leading to atherosclerosis are closely related to altered permeability of the walls of the arteries. Lipids are deposited in the wall more rapidly than they are removed. Very recent studies indicate that familial Type II hyperlipoproteinemia has a molecular basis, and that it is due to a defect in lipoprotein clearance at the cell membrane receptor site. These studies provide further definition of familial disease associated with cardiovascular disease.

Studies on the transport of lipids to and from the arterial wall have been extended by the development of better techniques of isotopically labelling lipid and protein components of plasma lipoproteins to permit analyses of the mechanism of transport of these molecules into the arterial wall. Methods of determining alterations in "chemical barrier" and wall ultrastructure have also been developed.

The process of lipolysis is central to the utilization of lipids by the body, and is a major determinant of blood lipid levels. The part played by various enzymes in the arterial wall during this process is being explored. Lipoprotein lipase has been the subject of intensive study almost continuously since its discovery at the NHLI 20 years ago. It has now been shown that there are at least two different lipases that can be liberated into blood to hasten lipid removal. Lipoprotein lipase is selectively absent in familial Type I hyperlipoproteinemia leading to abnormal levels of lipid in the blood. The previous observations on the rapid and reversible effect of insulin on lipids have been further advanced and it is now possible to study more directly the nature of the effects of insulin and adrenal hormones in the handling of lipids.

Hyperlipidemia is one of the major conditions associated with premature atherosclerosis, particularly coronary artery disease. The NHLI has been a leader in promulgating new systems of classification and identification of causes and treatment of hyperlipidemia.

In several of the Institute's Specialized Centers of Research in Arteriosclerosis, improvements are now being made in invasive and non-invasive diagnostic methods for the recognition of atherosclerotic plaques in the blood vessels.

Nutritional factors are believed to play an important role in the development of arteriosclerosis, and studies are in progress to clarify the role of these factors. The Multiple Risk Factor Intervention Trial, currently being implemented, has a strong nutritional component with the objective of reducing elevated serum cholesterol by adherence to a lipid-lowering diet, and in certain cases, weight control and correction of obesity. In addition, reduced intake of total carbohydrate and alcohol will be advised for men with elevated serum triglycerides who fail to respond to the basic diet.

A detailed nutritional questionnaire and diet recall are included in the prevalence studies conducted by the Institute's Lipid Research Clinic Program. A central computerized data system has been created to evaluate the role of diet in hyperlipidemia and the association of diet with the incidence of cardiovascular disease. The relationship of nutritional factors to lipid metabolism and development of atheroclerosis is being studied by many scientists, primarily in the Institute's Specialized Centers of Research in Arteriosclerosis.

The clinical investigations within the program on arteriosclerosis are varied, complex, and broad in scope. The recent progress highlighted here only refers to some of the major efforts underway and does not, by far, reflect the total Institute effort. The prevalence of and mechanisms behind the human forms of hyperlipidemia are now being studied at 12 extramural Lipid Research Clinics. The clinics are initiating an in-depth study of the relatives of patients found to have primary hyperlipoproteinemia during the prevalence studies. They are also evaluating the feasibility of using placental cord blood for the early diagnosis of hyperlipidemia. A Primary Prevention Trial is underway to test whether or not lipid lowering can prevent or delay the onset of overt cardiovascular disease.

Twenty clinics, a coordinating center, and a central EKG and chemistry laboratory are involved in another primary prevention trial, the Multiple

Risk Factor Intervention Trial. This trial seeks to determine whether, for men at above average risk of death from coronary heart disease (because of hyperlipidemia, hypertension, and cigarette smoking), a special intervention program will result in a significant reduction in mortality from coronary heart disease.

Two extensive studies of patients with the most common form of hypercholesterolemia (Type II hyperlipoproteinemia) have been completed. One study involved analysis of over 200 children born of parents with a form of familial hypercholesterolemia. The genetic data indicated a clear-cut mode of inheritance determined by a single gene and manifested early in childhood. The companion analysis of over 1,000 relatives of affected patients is the most extensive such analysis ever undertaken of this genetic defect. This study provides striking evidence of the premature atherosclerotic risk of patients affected with this disorder.

A study is in progress to characterize with respect to cardiovascular risk factors the familial and genetic associations of offspring of 1,644 spouse sets who were part of the original Framingham cohort. Preliminary results from the NHLI Twin Study indicate major genetic determinants of the observed variability in height, weight, blood pressure, and serum cholesterol. An offspring study is also in progress of the propositi of the Honolulu cohort of the Honolulu-Hiroshima-San Francisco Heart Disease Study.

The Coronary Drug Project, a secondary prevention clinical trial of lipid-lowering drugs has uncovered unfavorable features of two drugs, i.e., estrogen and dextrothyroxine.

The future challenges that face the Institute in the area of arteriosclerosis are many. In summary, the Institute plans to:

- Emphasize pathogenetic studies within existing research programs, centers of research, and lipid research clinics.
- Stimulate development of sensitive, specific, invasive and non-invasive diagnostic techniques for determining arteriosclerotic changes in blood vessels.
- Evaluate current techniques for diagnosis of hyperlipoproteinemia and other risk factors and develop better ones.
- Establish colonies of suitable animal models with particular reference to nonhuman primates with arteriosclerotic or hypertensive disease for use in research.
- Expand current population studies and clinical applications and prevention programs to include in-depth genetic studies.
- Encourage experts in psychology, sociology, and behavioral research to investigate the problems associated with health

education and attitudes, motivation, and compliance as these relate to the prevention of arteriosclerosis.

- Implement the Multiple Risk Factor Intervention Trial to determine whether, for men at above average risk of death from coronary heart disease, a special intervention program will result in reduction in mortality from coronary heart disease.

- Continue an intervention study in high-risk subjects to test the effectiveness of lowering the concentration of lipids by selected means to reduce cardiovascular mortality and morbidity.

- Provide for acquisition, analysis, and storage of data on the prevalence of different types of hyperlipoproteinemia, particularly in young age groups, with special emphasis on their relationship to diet and premature atherosclerosis.

- Promote further clinical, laboratory, and epidemiologic studies of personal attributes and life styles and their relationship to the development of arteriosclerosis, particularly with respect to the onset of arteriosclerosis in the young and in women.

- Expand current population studies and develop new epidemiological studies of the role of environmental factors in the pathogenesis of arteriosclerosis.

- Implement the US-USSR cooperative study to define the prevalence of different types of hyperlipoproteinemia.

Hypertension

Hypertension is one of the most commonly encountered forms of heart and blood vessel diseases, affecting an estimated 23 million adult Americans, or between 10 and 15 percent of the population. High blood pressure is the most important factor contributing to the development of strokes. It also accelerates the development of atherosclerosis in the coronary and peripheral vessels. Although hypertension is widely distributed among Americans, it has been found to be more common and severe among the black population, being three to four times that of whites in some age groups. High blood pressure can be controlled, and we know that such control results in reduced incidence of stroke and heart failure, kidney failure, and perhaps also a reduced incidence of heart attacks.

In more than 90 percent of the cases, the cause of hypertension is unknown; although the condition can be treated, it cannot be cured or prevented. The long-range goal in hypertension is to prevent it; the short-term goal is to optimize the utilization of effective treatment which currently exists.

Research on hypertension is a major effort within the Institute's program on heart and blood vessel diseases. The regulation of normal blood pressure is dependent upon striking a balance between a number of vasodilator and vasoconstrictor systems and studies are underway on each of these systems to identify their roles in hypertensive disease and to define the interrelationships between them.

Kallikreins are potent endogenous vasodilators. Recent studies have shown that normal individuals excrete on the average twice as much kallikrein in the urine as patients with essential hypertension. These patients appear to have reduced basal activity of the kallikrein-kinin system and also reduced responsiveness to physiologic stimuli.

The renin-angiotensin-aldosterone system is a vasoconstrictor one. During the past year radioimmunoassay procedures have been developed which are very specific, sensitive, and reproducible. Normal levels of plasma renin activity (PRA) have been established and it has been shown that urinary and plasma kallikrein levels can be dissociated from PRA. It has also been demonstrated that a centrally acting antihypertensive drug, alphamethyldopa, is capable of lowering PRA.

The prostaglandins have potent effects on the blood vessels. A radioimmunoassay has been developed which makes it possible to determine very small amounts of these substances in the plasma and urine. Catecholamines and the adrenergic nervous system have profound effects on blood pressure and renal function. Studies show that infusions of salt to normal humans cause an increase in dopamine, a decrease in norepinephrine, and a decrease in dopamine β-hydroxylase. This enzyme plays a key role in the maintenance of the salt and water balance of the body.

In the past year, unusual success has been achieved in the development of assays needed to carry out the complex biochemical studies needed for the investigation of factors relative to hypertension. Specialized laboratories are working on various assays of angiotensin, aldosterone, and prostaglandins to determine more fully the role of each in the pathogenesis and etiology of hypertension. Clinical tests are in progress of an agent which blocks the conversion of Angiotensin I to Angiotensin II. Since Angiotensin I is inactive on blood vessels while Angiotensin II is a vasoconstrictor, it will be possible to measure the effect on blood pressure when one effector is eliminated. If this test proves to be as useful as anticipated, more laboratories will be encouraged to use it in their studies.

Epidemiological data are being developed through the Hypertension Detection and Follow-up Program, which began its operational phase in 1973. Population data from 14 communities will become available to characterize prevalence of hypertension by a number of demographic, socioeconomic, and occupational characteristics. Follow-up of the 5,000 participants in the Regular Care Group will provide general population data on the progression of hypertension and its sequelae. An important component of this study involves behavioral research as it relates to the identification of factors which enhance adherence to therapy or impede such adherence.

Data on hypertension are now available from six prospective epidemiological studies in populations which have had follow-up observations and blood pressure measurements over 5 to 18 years. Systematic analysis of these data is underway.

An increasing number of research projects deal with the role of stress in the genesis of hypertension. A pilot clinical trial of antihypertensive therapy in mild hypertension is being developed in collaboration with four VA hospitals.

An intensive study of the pharmacokinetic actions of antihypertensive agents is underway. It appears possible that therapy may soon be tailored to the functional aberrations found in an individual hypertensive subject.

While it is well established that drug therapy to control blood pressure reduces the incidence of strokes and heart failure in cases of moderate and severe hypertension, only about 12 percent of hypertensives in the United States are currently receiving adequate treatment. A National High Blood Pressure Education Program has been initiated to help reduce the morbidity and mortality from hypertension and its sequelae by making the public and the medical profession aware of the problem and to motivate patients with hypertension to adhere to prescribed therapy. The NHLI has lead responsibility for coordinating this interagency, Federal/non-Federal cooperative effort.

Future challenges in hypertension range from efforts to determine its causes, the development of new therapeutic modalities, and programs to improve the application of available treatment. Specifically, the Institute plans to:

- Emphasize research on the etiology and pathogenesis of hypertension, including its epidemiology.
- Implement clinical trials of antihypertensive therapy in mild and labile hypertension.
- Evaluate new pharmacologic approaches to the treatment of hypertension utilizing existing research centers and pharmacologic expertise.
- Continue the Hypertension Information and Education Program to expand public and professional knowledge of the dangers of high blood pressure and the benefits of effective treatment.
- Establish an education research program aimed at testing hypotheses that will lead to new knowledge in methods of education to make the public aware of and motivated to deal with the problems of hypertension.

Cerebrovascular Disease

Cerebrovascular disease due to arteriosclerosis and especially due to hypertension is the basis for the great majority of strokes. The individual and public health burden of death, paralysis and brain damage is large. Of the 1.7 million adults who have this disease, 700,000 are partially or completely disabled. Stroke kills about 200,000 persons a year, more men than women, and at a greater rate among blacks than whites. While the National Institute of Neurological Diseases and Stroke is primarily responsible for programs on those aspects of stroke that deal with brain injury and its consequences, the NHLI is responsible for programs on the cerebrovascular pathology that underlies the stroke.

The goal of the NHLI program is to decrease the incidence of stroke through improved understanding of the pathology and pathogenesis of cerebrovascular disease. To determine the etiology and prevention of stroke, we need to conduct animal studies of the effects of chronic arteriosclerosis and chronic hypertension on the arteries of the brain. Little knowledge is available as yet about chronic changes in animal models, particularly in nonhuman primates appropriate for neurological examination. The goals of these animal studies will be to elucidate, by methods not applicable to man, the vascular pathology that leads to stroke.

Insofar as cerebrovascular disease is closely related to arteriosclerosis and hypertension, the future challenges discussed in the sections on Arteriosclerosis and Hypertension also apply to Cerebrovascular Disease. Specifically, the Institute plans to:

- Initiate studies in animals of the pathology of the lesions of chronic atherosclerosis and hypertension in the cerebral arteries. Emphasis will be placed on those lesions that may contribute to ischemic stroke or arterial brain hemorrhage.

- Continue prospective epidemiologic studies dealing with the identification of environmental factors and personal attributes which predispose to increased risks of stroke.

Coronary Heart Disease

Coronary heart disease is the major manifestation of atherosclerosis. It is the predominant form of heart disease in the adult American and causes 1.25 million heart attacks a year, and is responsible for chronic illness in 4 million Americans, 2.5 million below the age of 65.

A primary goal of the National Program is to develop information that will lead to improved diagnosis, prevention, therapy, rehabilitation, and understanding of the mechanisms resulting in symptomatic coronary disease. A second goal is to establish the indications for and the effects of coronary artery surgery in the treatment of various forms of coronary heart disease. A third goal is to develop and assess emergency medical care methods for heart attack victims and to develop and evaluate prophylactic treatment with drugs to prevent sudden cardiac death. A fourth major goal is to assess the needs and opportunities for cardiac rehabilitation with respect to physical, physiological, and societal factors to prevent disability and to bring back into the mainstream of life those who have suffered cardiovascular disease.

Of the five major and well-established risk factors for coronary artery disease, namely age, male sex, high blood lipids, high blood pressure and cigarette smoking, the latter three can be modified, and two of these are known to result in reduced cardiovascular risk when deliberately decreased. Cessation of cigarette smoking will decrease the enhanced risk of heart attacks among smokers, and reduction of moderate or severe hypertension reduces stroke and some other complications of high blood pressure. Its effect on heart attack or sudden cardiac death is unknown but may be appreciable. The Institute has implemented three large-scale trials to evaluate the cardiovascular effects of risk factor modification. These are described in the previous sections on Arteriosclerosis and Hypertension. Within this decade, we should know the impact of lowering lipids on heart attack in certain types of hyperlipidemias, the impact of controlling hypertension on heart attack, as well as the impact of controlling simultaneously the three major risk factors.

Plans have been developed for Specialized Centers to conduct research on the various manifestations of coronary heart disease. A Collaborative National Study on Coronary Artery Surgery is in progress and a US-USSR Cooperative Study on Management of Ischemic Heart Disease is under development.

Pilot testing of antiarrhythmic drugs to be given to patients following hospitalization for acute myocardial infarction is progressing satisfactorily and studies have begun of early administration of prophylactic antiarrhythmic drugs in emergency care settings. A task force has been convened to assess the needs and opportunities for the physiological, psychological, and societal rehabilitation of patients with cardiovascular disease.

Past scientific research has provided the base for the current treatment of heart attack, specifically relief of pain and prevention or reversal of rhythm disturbances which can be lethal. Recent investigations have shown that the size of the infarct is directly related to death or disability from a heart attack. Studies are currently underway to develop better ways to assess infarct size as well as to assess therapies for limiting the size of infarcts. Recent animal experiments show that inhalation of oxygen decreases the infarct size. The use of a pump to assist the heart has been shown to relieve pain, and if applied early in the course of attack, limits the amount of heart muscle destroyed. In combination with certain drugs, the effect is even more striking.

For the future the emphasis in patient-oriented research must shift from its current focus upon acute heart attack to the inclusion of other important aspects of coronary heart disease--angina pectoris, heart failure, arrhythmias, and sudden death. Specifically, the Institute plans to:

- Establish approximately 12 specialized units to conduct research on the various manifestations of coronary heart disease.
- Establish a collaborative national program to determine the indications for and the long-term effects of coronary artery surgery in the management of coronary heart disease.
- Implement the US-USSR cooperative study on the management of ischemic heart disease by medical and surgical techniques.
- Promote studies to elucidate the mechanisms and factors which precipitate acute coronary events and to determine the characteristics of individuals at highest risk for these events.
- Promote studies on the prodromata of acute coronary events.
- Develop and test techniques of emergency cardiovascular diagnosis and therapy.
- Design, pilot test, and subsequently implement large-scale trials of chronically administered antiarrhythmic drugs in patients at high risk for sudden cardiac death.
- Implement the US-USSR cooperative program on the prevention of sudden cardiac death.
- Design, pilot test, and subsequently implement large-scale trials of the early administration of prophylactic antiarrhythmic drugs immediately upon the development of heart attack symptoms.
- Assess the needs and opportunities for cardiac rehabilitation in terms of physical, psychological, and societal factors, and implement appropriate programs of research.

Peripheral Vascular Disease

Peripheral vascular diseases are the cause of considerable suffering and disability. Surgeons have developed techniques to replace diseased peripheral artery segments with vascular or prosthetic grafts.

The goals of the Institute's programs in this area are to improve diagnosis, therapy, and rehabilitation, and to improve understanding of the mechanisms causing peripheral arterial, venous, and lymphatic diseases. The bulk of developments related to Peripheral Vascular Disease is described in the section on Arteriosclerosis.

Methods must be developed for diagnosing peripheral vascular disease before they reach an advanced state, for more effective medical management, and for extending surgical therapy to small vessels. Understanding the basic cause of the diseases is most important and will require study of the role of neural control of vascular tone, mechanism of action of smooth muscle, pathogenesis of peripheral atherosclerosis, and the importance and signifiance of risk factors. The future plans of the Institute are to:

- Encourage clinical, laboratory, and epidemiological research into the causes, diagnosis, and treatment of diseases of the peripheral arteries, veins, and lymphatics

- Implement related programs described in the section on Arteriosclerosis, and the programs on non-invasive instrumentation discussed in the section on Bleeding and Clotting Disorders under Blood Diseases and Blood Resources.

Arrhythmias

Important new concepts are developing about the correlation of arrhythmia and the extent, severity, and prognosis of heart disease. Information is being accumulated about the different causes of arrhythmias and their differential responses to drug therapy. However, most of the drugs currently effective in the treatment and control of arrhythmias have side effects which limit their applicability.

Identification of arrhythmias that carry a high risk of sudden cardiac death is fundamental to preventive measures. The analysis of spontaneous rhythms and the influence of drugs must be assessed by quantitative analysis of extensive electrocardiographic tape recordings. Substantial progress has been made toward performing this task automatically, rapidly, and quantitatively by computer.

A major goal of the Institute's program is to develop methods for the prevention of arrhythmias which specifically cause sudden cardiac death. Another goal is to improve currently available methods for prevention, diagnosis, and management of arrhythmias and other electrical disturbances of the heart. Clinical studies are in progress to identify chronic or intermittent disturbances of rhythm, and several projects are primarily directed at the electrophysiology and therapy of rhythm disturbances associated with inadequate blood supply to the heart. A collaborative study is being developed to describe significant arrhythmias in specific groups of patients and their modification by drug therapy. A previously undefined syndrome of potentially major clinical importance has recently been described. This is the Primary Ventricular Fibrillation Syndrome or the Instantaneous Death Syndrome. Pathologically, the syndrome is characterized by severe chronic coronary artery disease, absence of recent coronary artery lesions, and no evidence of recent myocardial necrosis. This syndrome may comprise up to 50 percent of all cases of sudden cardiac death. The recognition of this new syndrome presents a challenge for preventing premature death from coronary artery disease.

The future plans of the Institute are to:

- Expand current programs for the prevention of arrhythmias causing sudden cardiac death, focusing particularly upon the electrophysiology and therapy of arrhythmias associated with inadequate blood supply to heart muscle and upon clinical studies to identify chronic or intermittent arrhythmias which indicate an increased risk for sudden death.

- Augment the development of automated, quantitative techniques for analyzing electrocardiographic rhythm signals to facilitate clinical investigation of arrhythmias.

Heart Failure and Shock

Heart failure and shock represent major causes of death and may be the end result of many different diseases. The amount of irreversibly damaged myocardium is not predetermined at the onset of myocardial infarction; there is a zone which is in jeopardy but has not yet progressed to the point of no return. Current research has identified several promising means for protecting this zone of potentially reversible damage and for promoting its recovery. Some of these approaches are being investigated in initial clinical feasibility trials; other promising techniques are being tested in animal studies.

Methods to quantify the amount of heart muscle which is inadequately perfused or which has undergone irreversible damage are crucial to the evaluation of therapeutic interventions. Recently, several such methods have shown promise. They may make it possible to test new approaches more economically and in fewer patients than is now required for evaluation by gross clinical criteria.

Other aspects of the diagnosis, etiology, therapy, and prevention of heart failure and shock warrant emphasis. These include research on improving the pumping function of the myocardium, as well as understanding and treating the disturbances of the regulation of peripheral blood vessels, the related endocrine functions of the body, and the renal functions.

Current therapy to enhance the survival of ischemic myocardium must be evaluated on a larger scale by more definitive clinical studies than those now underway. The Institute plans to:

- Enlarge biochemical and physiological studies of the fundamental processes associated with myocardial survival both in laboratory and clinical studies.

- Establish clinical studies, contingent upon success of current pilot studies, to assess the therapeutic efficacy of promising techniques for minimizing the extent of myocardial damage.
- Expand program for quantifying the extent of myocardium which is inadequately perfused or which has undergone irreversible damage.
- Implement the US-USSR cooperative program on myocardial metabolism.

Congenital and Rheumatic Heart Diseases

Congenital and rheumatic heart diseases are important disorders of childhood, and may form the basis for considerable impairment of the quality of life of the patient surviving into adulthood. The earliest surgical successes in the treatment of heart diseases were in the correction or palliation of congenital heart disease. These successes are being expanded in the development of diagnostic and surgical techniques applicable to the newborn. Important insights have also been gained into the development of the cardiovascular system. However, in most cases, we still do not know what makes the heart develop abnormally before a baby is born.

Rheumatic heart disease is an immunological disturbance that frequently occurs after initial rheumatic fever and prior streptococcal infection. It not only can shorten life, but also seriously impair the quality of life. Improved understanding and control of immunological problems could thus be important in the identification of susceptibility and the prevention of rheumatic heart disease, as well as in the success of cardiac transplants and in the prevention or treatment of cardiomyopathy and possibly other forms of heart disease.

The Institute has maintained a continuing long-term effort focused upon all facets of the problems of congenital and rheumatic heart disease, resulting in a steady improvement in the clinical management of these patients. Extremely delicate operations that were inconceivable a few decades ago are now performed routinely in most of the major medical centers. It is now possible to perform very complex repair of the heart even in young infants.

Essential to the prevention of congenital heart disease is a better understanding of the normal development of the cardiovascular system and the causes of abnormal development. The future plans of the Institute are to:

- Establish Specialized Centers of Research in Congenital Heart Disease at two to four locations in FY 76. The research in these Centers will emphasize such topics as cardiovascular development and improved diagnostic techniques and therapy, particularly in the newborn.

- Implement a targeted effort to study immunological problems in heart disease and their management, specifically in relation to rheumatic heart disease, cardiac transplantation, and cardiomyopathies.

- Implement in US-USSR cooperative program in congenital heart disease.

Cardiomyopathy and Infections of the Heart

Cardiomyopathy and infections of the heart cause cardiomegaly, arrhythmias, and occasionally sudden death. They are the result of a variety of factors. Known factors include toxic substances, viral infections, alcohol, immunological phenomena, nutritional deficiencies, muscular dystrophy, and a number of rare diseases. Cardiomyopathies, myocarditis, endocarditis, and pericarditis are increasing in frequency. However, quantitative information concerning the prevalence of these diseases is not available because we still lack specific diagnostic criteria and laboratory tests. Future plans of the Institute in this program area will:

- Focus attention of studies of the etiologies of cardiomyopathies and infections of the heart.

Circulatory Assistance

Present and foreseeable techniques of general and pharmacological management of acute and chronic cardiac insufficiency and shock still leave a substantial fraction of patients with compromised or fatally impaired heart function. By mechanical supportive means, it is possible to substitute for some of the pumping function of the heart and to relieve its workload. Presently, such techniques are possible briefly in man and for longer periods in the experimental animal.

Partial and totally implantable left ventricular assist devices may be significant in the future in terms of correcting acute and chronic cardiac insufficiency. In recent experiments, a left ventricular assist device has performed successfully in vivo in calves. Left ventricular assist with intra-aortic balloon counterpulsation was introduced into clinical studies about a decade ago. Studies have shown that this form of mechanical assist can temporarily reverse shock in subjects refractory to all forms of medical therapy, permitting additional diagnostic and therapeutic procedures. The overall impact of this form of therapy in patients with acute myocardial infarction, however, remains to be determined. Recent patient studies have shown a definite reduction of infarct size associated with the use of this mechanical device. This reduction of infarct size, which previously could only be demonstrated in animal studies, may represent a promising method to decrease subsequent patient morbidity and mortality.

Mechanical techniques for augmenting or substituting for the performance of the heart must be expanded to encompass emergency temporary devices for short-term management, extracorporeal assist pumps for intermediate periods of use, long-term implanted heart assist devices, and total cardiac replacements. The Institute plans to:

- Continue the research, development, and assessment of emergency temporary, circulatory support devices directed at short-term management of heart failure and shock to stabilize the clinical condition and permit its reversal.
- Expand the research, development, and assessment of implantable heart assist devices capable of taking over a significant fraction of the work of the heart for extended periods of time.
- Undertake research, development, and assessment of external heart assist devices capable of taking over a significant fraction of the work of the heart, and requiring minimal surgery for connection and removal.
- Expand research, development, and assessment of implantable heart replacement devices for permanent implantation.
- Expand research and development of circulatory assist and artificial heart systems, including the development of compatible biomaterials, appropriate pumps, actuators, energy transforming devices, implantable energy systems, transcutaneous transmission of energy, and control systems for the devices.
- Expand research and development of noninvasive and invasive instruments and techniques for the assessment of cardiovascular performance.

Lung Diseases

Lung diseases covered by the National, Heart, Blood Vessel, Lung, and Blood Program account for an estimated 150,000 deaths each year in the United States, cause 60 million days lost from work, 40 million days of bed-restricted activity, and cost the economy about $6 billion a year in lost productivity and wages and medical care costs.

Structure and Function of the Lung

Our current capability to deal with the problems of lung diseases in the United States is severely limited by our lack of fundamental knowledge about the lung. This knowledge must be gained before truly definitive preventive and therapeutic measures can be designed. Current remedies are not only very costly but are also only temporary, stopgap techniques which need to be replaced by more specific and longer term methods yet to be discovered through research. Thus, the most important priority now in the Institute's lung diseases program is to expand research on the lung and its biology in order to identify factors critical to the health of the lungs.

Recently, a major step has been taken toward an understanding of lung disease mechanisms. The lung is made up of about 40 different types of cells. Recent progress in studies at the cellular level has contributed to understanding relationships between lung structure and function. Studies have advanced to the point that it should be possible to describe the multiple functions of the various types of lung cells in terms of cellular and biochemical changes associated with different respiratory diseases. However, before such abnormalities can be understood, it is necessary to have a firmer knowledge of normal lung cell structure and function. This is a difficult research task because of the multifunctional nature of the lung and because of the various roles performed by different lung cells. Recently, an enzymatic procedure has been developed for dispersing lung tissue into separate viable cells, thereby providing an opportunity to isolate and culture individual cell populations from whole lung tissue.

The next several years of research will provide information relating structural and biochemical characteristics of individual lung cells. As this information develops, investigations into the molecular basis of lung disease should be possible. This is an essential step toward effective prevention and treatment. The future plans are to:

- Encourage investigator-initiated research in metabolism, cellular biology, and defense mechanisms of the lung.
- Develop multidisciplinary approaches in the area of normal lung structure and function.
- Seek new information on the structural components of the lung.

Pediatric Pulmonary Diseases

Among childhood diseases of the lung, cystic fibrosis, and hyaline membrane disease are health problems of national significance. Hyaline membrane disease is the most common cause of death in the United States, and affects between 50,000 and 100,000 babies each year, about half of whom die. Bronchiolitis, also covered in the National Program, is one of the major obstructive airway diseases of children and may be important in the development of adult chronic lung disease. The cause of hyaline membrane disease in the newborn, the nature of cystic fibrosis, and the possible long-term effects of early childhood bronchiolitis need to be determined and understood.

Two important breakthroughs have occurred in the detection and treatment of hyaline membrane disease. First, it is now possible to detect the disease before birth. Secondly, a therapeutic breakthrough has occurred which significantly reduces the mortality from this disease. This therapy, known as continuous positive airway pressure, is used in conjunction with artificial ventilation, and has resulted in survival of up to 90 percent of these babies, compared to about 50 percent in the absence of such therapy.

Understanding the biochemistry and molecular biology of surfactant during normal maturation and hyaline membrane disease in order to develop methods of modifying or preventing the disease is a major challenge for the future. The cause of the mucus abnormalities in cystic fibrosis and the pulmonary derangements which result must be discovered before effective and meaningful therapeutic and preventive measures can be undertaken. As a first step in determining whether bronchiolitis in childhood predisposes to chronic lung disease in the adult, criteria for diagnosis of bronchiolitis and protocols for long-term study need to be established. The future plans of the Institute are to:

- Extend interdisciplinary studies of biochemical changes associated with hyaline membrane disease through Specialized Centers of Research. In addition, programs will be initiated to study biochemical changes associated with the development of cystic fibrosis.

- Test various supportive measures for patients with cystic fibrosis, including mist-tent therapy and bronchodilators.

- Improve management and therapy of hyaline membrane disease through the development of programs for rapid transfer of infants with this disease to intensive care units.

- Initiate epidemiologic studies to determine prospectively the long-term effects of bronchiolitis in childhood on the occurrence of chronic lung disease in the adult.

Emphysema and Chronic Bronchitis

Chronic obstructive pulmonary disease (COPD) is a major health problem in the United States. Each year, direct and indirect costs of COPD amount to approximately $1.8 billion and 90,000 man-years of lost productivity. Emphysema and chronic bronchitis are the two main diseases which, when considered together, are referred to as COPD. Both emphysema and chronic bronchitis produce breathlessness, cough and increased susceptibility to respiratory failure and death. COPD attacks middle-aged men and women and is particularly common in smokers. It is now believed that early abnormalities (physiologic and biochemical) related to emphysema and chronic bronchitis may be detected to a stage when lung damage is still reversible.

Emphysema is the fastest growing cause of death in the United States and is now the third leading cause of death from respiratory disease. The NHLI is currently placing major emphasis on effects to identify the risk factors of COPD. There are many different kinds of emphsema, none well understood. Cigarette smoking has long been recognized as a major risk factor for emphysema, but attempts to identify other causes and risk factors have often ended in failure. New lines of research have opened up through the recent discovery of a genetic basis for one type of emphysema. Environmental risk factor are being identified in a variety of occupations.

Early detection is an important step toward prevention of COPD. A new method has been developed for the early detection of changes in lung function and structure which appear to be the first sign of chronic obstructive pulmonary disease. This method, measurement of closing volume, detects early changes in the lung which are thought to eventually progress to the clinical signs and symptoms of COPD. It is presently believed that in persons with abnormal closing volume measurements, but with otherwise normal lung function tests, the progression of disease may be reversed and the development of disabling disease prevented with proper treatment and the cessation of smoking.

The Institute's plans for the future are to:

- Develop multidisciplinary program addressed to the problem of smoking. This program will include investigation of the mechanisms and agents responsible for cigarette smoke injury in emphysema and chronic bronchitis.
- Elucidate the role of host factors, including genetic ones, in the development of emphysema and chronic bronchitis.
- Enlarge efforts in emphysema and chronic bronchitis prevention through the development of improved techniques and devices for early detection of reversible diseases and application of new knowledge from studies of risk factors and their control.
- Initiate controlled clinical trials to evaluate the efficacy of current and newly developed approaches to therapy and rehabilitation.

Fibrotic and Immunologic Lung Diseases

Fibrotic and immunologic lung diseases result from the interaction of a variety of environmental and host factors. These include viral and bacterial infections, diseases of the connective tissue, radiation damage, exposure to substances such as molds and dust that initiate hypersensitivity reactions, and inhalation diseases resulting from exposure to substances such as coal dust, silica, asbestos, and pollutant gases such as nitrogen dioxide, ozone, and sulfur dioxide.

Fibrotic and immunologic lung diseases can be prevented or treated if the offending substances can be removed or their effects suppressed.

Early diagnosis of fibrotic and immunologic lung diseases, while they are still reversible and curable, is a primary research objective.

The Institute's plans for the future are to:

- Seek new information about the synthesis and degradation of collagen and the immunologic responses and defense mechanisms of the lung through continued and extended multidisciplinary programs.
- Initiate programs to develop pharmacologic agents that will modify the alterations in connective tissue metabolism that lead to pulmonary fibrosis, and study the use of immunologic techniques to stimulate tissue defense mechanisms against immunologic lung diseases.
- Initiate epidemiologic studies to investigate etiologic factors in population groups characterized by unusual prevalence of fibrotic and immunologic lung diseases.
- Develop a program of education of physicians and the lay public with regard to environmental agents implicated in pulmonary fibrosis and immunologic lung diseases.

Respiratory Failure

Respiratory failure may occur in many different disorders, both acute and chronic, pulmonary and nonpulmonary. Despite considerable progress in the development of sophisticated therapy, respiratory distress syndromes of the adult remain among the most common causes of postoperative mortality and of death related to major trauma. Because acute respiratory insufficiency is potentially reversible if recognized early and if treatment is initiated promptly, the major research emphasis at present is on identification of factors that predispose to these syndromes, studies of the effects of oxygen toxicity, and development of therapeutic devices, especially ventilatory assist devices and oxygenators. (See section on Respiratory Assistance)

Various techniques and devices have been developed for detecting impending respiratory failure. A sensitive spirometer that measures the peak acceleration which occurs early in forced expiration is currently being evaluated for its ability to detect early airway obstruction. Methods have been developed and are being evaluated for assessment of the degree of pulmonary edema. Powdered tantalum, as a roentgenographic contrast medium, has been clinically used to study the structure and function of bronchi, bronchioles, and alveoli in diseased lungs.

The specific challenges in this area are to improve the devices and techniques used to detect potential respiratory failure and to provide the attending physician with a better description of lung function during respiratory failure. The Institute plans to:

- Initiate development of devices and techniques for monitoring of respiratory function in patients with impaired lungs.

- Develop and test improved invasive and noninvasive instruments for blood and respiratory gas analysis in patients with lung disease.

- Develop devices and techniques to detect and monitor resistance in small airways and structural and functional abnormalities of diseased lung.

Pulmonary Vascular Diseases

Pulmonary vascular diseases, which include cor pulmonale, pulmonary hypertension and pulmonary edema, are serious lung disorders with often devastating consequences. Reliable data on incidence and prevalence of pulmonary vascular diseases, as well as on the effectiveness of present modes of therapy, are not available. This is largely because present methods for diagnosis and for assessing therapeutic progress involve procedures that cannot readily be used on very ill or large numbers of patients.

Early diagnosis is the first step in treating these pulmonary vascular diseases effectively while they are still reversible. The Institute plans to:

- Extend multidisciplinary efforts to elucidate the dynamics of exchange of water, protein, and electrolytes, the biochemistry of edema fluid, and metabolic alterations in the edematous lung.

- Encourage the development of safe, noninvasive methods for detecting pulmonary hypertension, cor pulmonale, and pulmonary edema.

- Promote multidisciplinary approaches on the pathogenesis and pathophysiology of cor pulmonale and pulmonary hypertension.

- Develop epidemiologic programs aimed at determining the true impact of cor pulmonale and pulmonary hypertension on the population.

Inhalation Diseases

This program area is addressed to respiratory diseases that result from the direct effects of inhaled dusts, vapors, or gases and which can be prevented by removal of the offending substances or by protecting individuals from them. Therefore, a primary goal of this program is to disseminate information about the causes of these diseases and how to avoid them. The research goal is to improve detection of the known causes of these diseases and thereby prevent their development.

Not long ago, the hazard of pneumoconioses was considered confined to certain jobs in specific occupations. Today, it is recognized that the problem is far more complicated and that sources of these diseases have greatly widened.

The Institue plans to:

- Develop programs to improve the prevention, detection, and relief of inhalation diseases.

Respiratory Assistance

The development of techniques and devices for providing respiratory assistance is an important component of the Institute's research efforts to combat all diseases of the lung, and especially respiratory failure. The most significant progress in this program area to date has been the development and testing of membrane oxygenators in animals and humans. These oxygenators have demonstrated sufficient promise to warrant testing in clinical trials under highly controlled conditions. If such trials demonstrate the efficacy of the devices, they could become a valuable mode of therapy to be widely used in support of infants with respiratory distress syndrome and adults in respiratory intensive care units. Research on respirators have led to development of a compact, portable, ventilatory-assist device which can be patient-cycled for the changeover from the expiratory to inspiratory phase. Clinical trials are presently underway.

The Institute plans to:

- Expand programs addressed to ventilatory-assist devices and oxygenators to insure improvements in available devices and development of new ones.

- Test presently available and promising new devices in controlled clinical studies.

- Develop programs to insure the early initiation of treatment.

- Continue and extend Specialized Centers of Research where sophisticated techniques are available in order to capitalize on what is known and to improve present modes of therapy.

Blood Diseases and Blood Resources

The NHLI program in Blood Diseases and Blood Resources is intimately related to the Institute's responsibilities in cardiovascular and pulmonary diseases. Problems in the blood are often reflected in disorders of the cardiovascular and pulmonary systems. Life-threatening situations can arise if the blood clots within the heart, blood vessels, and lungs, or if it escapes from the cardiovascular system, as in hemorrhage, into the tissues or outside of the body. Blood that has lost its capacity to clot, such as in hemophilia can also give rise to life-threatening situations.

Blood is a very important life-saving therapeutic tool in medicine as well as in surgery. Millions of Americans are saved each year by blood or blood component therapy. Many of these individuals would previously have met with certain death. Almost 10 million units of blood and 1.7 million liters of plasma (the equivalent of an additional 8.5 million units of blood) were collected in the United States in 1971 for use in therapy.

Bleeding and Clotting Disorders

Blood clotting abnormalities are a major cause of death and disability in the United States. The National Program addresses two important areas related to disordered hemostatis: the hemophilias and the thromboembolic disorders. In the case of the hemophilias, life-threatening situations occur as a result of excessive uncontrolled bleeding because of failure of the patient's blood to clot normally. In the case of thromboembolic disorders, the opposite is true: the blood clots too readily, e.g., in the heart, the brain, or the lungs, causing complications such as heart attacks, strokes, or pulmonary embolism.

The hemophilias constitute a major national health problem for several reasons. First, treatment must be continued through the patient's lifetime at enormous costs; the alternative is crippling and death. Second, treatment of this single disease places one of the largest demands on the nation's blood supply. Finally, the impact of this disease on the patient and his immediate family is catastrophic in terms of social, psychological, and economic costs.

Research advances in the last two decades have completely changed the outlook for hemophilia care. The clotting factors needed by the hemophiliac have been identified, partially characterized and can now be produced from normal donor plasma.

Additional progress can be expected in the medical management of hemophilia. The Institute plans to:

- Support fundamental research on hemophilia, especially on the molecular structure of the clotting factors, the chemistry of plasma fractionation, and the physiology of the coagulation system.

- Establish Specialized Centers of Research for the bleeding disorders.

Thrombosis and embolism are often responsible for the crippling or lethal manifestations of heart and blood vessel diseases. They are implicated in several of the major causes of death in the United States. Arterial thrombosis plays a role in heart attacks, stroke, and chronic renal disease. Venous thrombosis can result in pulmonary embolism, a disorder which hospitalizes some 300,000 persons and contributes to the death of more than 50,000 patients annually. Thrombosis and hemorrhage in the microcirculation play primary or contributory roles in hypertension, stroke, diabetes, cancer, sickle cell anemia, and many other disorders affecting virtually every organ in the body.

Risk factors for thrombosis and embolism have been recognized and high risk clinical situations have been identified. It is clear for instance that patients suffering from hip fracture or undergoing hip surgery are at a very high risk for venous thrombosis and subsequent pulmonary embolism. Patients, especially the elderly, who are immobilized for any cause are at high risk. Venous thrombosis commonly occurs as a complication of heart failure.

Work in the last decade on the clot-dissolving agents, urokinase and streptokinase, demonstrates that these agents have an important potential as treatments for a wide range of thromboembolic disease. For example, it has been demonstrated that these agents significantly accelerate the resolution of clots in the lungs (pulmonary embolism).

Further efforts are needed to capitalize on past progress in research on thrombosis and embolism. The Institute plans to:

- Encourage fundamental research in thrombosis and in the relationship between thrombosis and atherosclerosis.

- Support the development of techniques and instrumentation for sensitive, reliable, specific detection of thromboembolic disease.

- Devise and support clinical trials of platelet-inhibiting drugs in the prevention of thrombosis in patients at high risk.

- Conduct clinical trials of the efficacy of clot-dissolving drugs in the treatment of thromboembolic disorders, especially heart attacks.

Sickle Cell Disease and Related Disorders of the Red Blood Cell

This group of programs includes sickle cell anemia and sickle cell trait, conditions closely related to sickle cell disease such as Cooley's Anemia, and defects affecting the red blood cell membrane and enzyme systems.

Sickle cell trait, the most common inherited disorder in the United States, is believed to be present in more than 2 million U.S. citizens, primarily black. The trait is a relatively benigh "carrier" form in almost all of these 2 million persons. However, approximately 1 in every 500 black babies is born with the life-threatening form of the disease called sickle cell anemia. Such individuals undergo painful episodes called sickle cell crises.

Recent advances have been made in fundamental research on sickle cell disease. The disease is due to a genetically determined change in the hemoglobin. The presence of the changed hemoglobin (hemoglobin S) is accompanied by distortions in the shape of the normally biconcave erythrocytes, making these less able to survive in the blood circulation and less able to move freely through the smaller blood vessels.

The NHLI continues to coordinate the HEW Sickle Cell Disease Program initiated by the President in 1971. The major objectives of this program are: (1) to foster research and development both at the fundamental and clinical levels; (2) to initiate and expand community education, screening, and counseling programs; (3) to educate medical and allied health professionals about the problems of sickle cell disease; and (4) to improve clinical care for victims of sickle cell disease.

Despite knowledge of the precise defect in the sickle hemoglobin molecule, the areas of ignorance about sickle cell disease are probably greater than the areas of understanding. Therefore, a balanced program must address a variety of problems, from understanding of the erythrocyte to treatment of the patient and education of the community. The Institute plans to:

- Sustain and expand support of studies to understand better the molecular structure of sickle hemoglobin and interactions of other abnormal hemoglobins with sickle hemoglobin.

- Implement development and testing of improved techniques for screening and diagnostic testing of hemoglobin abnormalities.

- Develop, in collaboration with other Federal agencies, programs to provide accurate information on sickle cell disease and Cooley's anemia.

- Evaluate clinical approaches for the treatment of these disorders.

Cooley's anemia (thalassemia) is an inherited disease resulting from defective production of the hemoglobin molecule which in turn leads to rapid destruction of the patient's erythrocytes. On a worldwide basis, thalassemia is the most common inherited disease resulting from a single gene mutation. Reliable data on its prevalence in the United States are not available. However, it is estimated that it occurs in at least 5,000 Americans, largely of Mediterranean ancestry.

Several important advances have been made in this program area. A method has been developed to synthesize hemoglobin in a cell-free system using components isolated from human erythrocytes. This has subsequently led to the determination that the molecular defect in Cooley's anemia is transmitted by a messenger RNA. A biologically active messenger RNA has been isolated from bone marrow and peripheral cells in patients with beta thalassemia. Full understanding and subsequent control of this material may ultimately lead to the capability of controlling the error resulting in thalassemia.

We know a considerable amount about the molecular abnormality in Cooley's anemia, but we do not know how to correct it. Present treatment is limited to frequent transfusions. While this gives temporary relief from the anemia, it burdens the body with excess iron that cannot be eliminated. Future plans of the Institute are to:

- Continue efforts in Cooley's anemia in coordination with other Institutes at the National Institutes of Health and with other Federal agencies. These programs will include studies on the mechanism of hemoglobin synthesis, clinical research to determine the effect of splenectomy and transfusion programs on the course of the disease, development of agents for removal of excess iron, prenatal diagnosis, and better laboratory methods for detecting the carrier state.

Disorders of the red cell membrane and enzyme systems are responsible for a small but significant number of clinically important cases of anemia. Perhaps more importantly, the red cell provides an easily accessible model for studying physiologic mechanisms and metabolic controls common to many cell systems.

Progress is being made in a number of areas important to understanding the membrane and enzyme systems of erythrocytes. The properties of red blood cells which contribute to their viability and which support their physiologic function in the circulation are being explored. Also in progress are studies of physical properties such as deformability, adhesiveness, and viscosity.

The mechanism of anemia resulting from the interaction of drugs and agents with G6PD deficient red cells requires further study. Better understanding of the factors which regulate red cell metabolism is necessary in order to extend the preservation of red cells beyond a few weeks. The Institute plans to:

- Continue to support research on normal and abnormal red cell enzyme and membrane disorders, and identify reference laboratories for the diagnosis and investigation of these abnormalities.

Biomaterials

An understanding of the basic interactions between blood and the properties of natural and synthetic materials is essential to the development of implantable diagnostic devices, circulatory assist devices, oxygenators, and other artificial organs, as well as the understanding of the genesis of arteriosclerosis.

Several classes of biomaterials show both promising biocompatibility and suitable mechanical properties for use in circulatory assist devices and oxygenators as discussed in the sections on Circulatory Assistance and Respiratory Assistance, above.

Increased emphasis must be placed on the fundamental aspects of the interactions between blood and biomaterials. Improved biomaterials suitable for specific physiologic requirements need to be developed and improved techniques for modifying and grafting surfaces must be explored.

A better understanding of the mechanical and physiochemical properties of natural tissues needs to be developed so that this basic information can be used for the synthesis of new materials for specific biomedical applications. There is a tremendous future challenge in using the natural tissues as models to create synthetic systems with properties approximating those of the natural tissues. The Institute plans to:

- Support basic research into interactions of blood components with both synthetic materials and natural biopolymers.
- Explore the synthesis and preparation of a variety of biocompatible materials suitable for specific uses in medicine.
- Develop improved methods for the physicochemical and biological evaluation and characterization for biomaterials.

Blood Resources

The supply of blood and blood components is a critical national problem. Blood is a very important therapeutic tool. The demand for blood and blood fractions is increasing with no foreseeable limit except that dictated by the practical considerations of limited supply. In the face of an increasing demand and a limited supply of blood it is important that economical and efficient use be made of the available blood resources.

The present blood resources complex, while providing essential services and products, has not consistently maintained an adequate supply or achieved the highest attainable quality of blood therapy. The goals which the National Program recognizes in the provision of blood services to the people of the United States are to promote and maintain:

- Adequate blood supply
- Highest attainable quality
- Access to the supply for everyone in need
- Efficiency in the collection, processing, storage, and utilization of blood.

The Institute continues to collaborate with other Federal agencies and the private sector in order to foster the rapid implementation of a truly nationwide blood program. The Institute also continues to support research which will assist in the future implementation of a Blood Data Collection Center to supply comprehensive and continuous information on the supply, size, distribution, and use of blood and blood products.

The specific future challenge for both the NHLI and other government and private agencies is to encourage the development of an appropriate mechanism for implementing cost-effective systems and regionalization. Other important challenges are improved approaches to determine the utilization of blood and blood products for specific blood diseases and other clinical problems and to assess their immediate and future impacts. The Institute plans to:

- Coordinate its efforts with private and public organizations involved in blood banking in the creation of an all-voluntary blood donation system and regional integration to increase effectiveness.
- Assist in the implementation of a Federal Blood Data Collection Center.

In spite of rapid advances in the understanding of hepatitis, primarily serum hepatitis, there is still no way to ensure that blood from a given donor will not transmit this disease. The final test for hepatitis in blood may have to await the identification of new antigens or the development of an entirely new approach to testing, perhaps involving a bioassay method. Elimination of any chronic virus carrier state by some intervention technique is not possible at present. We are at present only able to define the carrier state without affecting its course.

Future challenges for fail-safe systems of donor-recipient identification on the national scale involve the general, large-scale acceptability of devices and the high cost of acquiring and maintaining them. The potential toxicity of plastics in contact with the blood needs further study. The Institute plans to:

- Participate with other agencies in a concerted attack on hepatitis

- Continue studies in the areas of toxicology of plastic devices having contact with blood and the evaluation of fail-safe donor-recipient identification.

Research is in progress to explore new methods of plasma fractionation to determine if the components presently being prepared can be recovered more efficiently and economically.

The medical demand for red blood cells, as distinguished from other blood components, sets the pace for the collection of whole blood. Patients who need red cells often do not need other components Currently, whole blood is used in more than three-fourths of all transfusions, although experts indicate that it is necessary in less than one-fourth of the cases. The Institute plans to:

- Support and participate actively with other interested organizations to insure that new fractionation methods are devised which would cope with the ever increasing demands on blood resources.

- Develop means to enhance and evaluate the appropriateness of blood utilization.

- Implement the US-USSR cooperative program on blood transfusion, particularly in relation to cardiovascular surgery.

NATIONAL LIBRARY OF MEDICINE

NATIONAL LIBRARY OF MEDICINE

Overall Goals and Strategies

The basic objective of the National Library of Medicine (NLM) is to promote the efficient dissemination of biomedical information. The world's largest research library in a single scientific or professional field, the NLM acquires relevant information from world-wide sources; organizes and distributes biomedical literature and audiovisuals; provides assistance to medical libraries to encourage a nationally coordinated approach to meeting local and regional information needs; and conducts programs of research and development to find better ways of transferring information in support of health research, education, and patient care.

A basic premise underlying all NLM activities is that the flowering of communications technology which has helped create the "information explosion" can also be used to help manage it.

The NLM has developed--and continues to emphasize--computerized systems for bibliographic information storage and retrieval, such as MEDLARS* and the newer MEDLINE (MEDLARS on-line). It has also explored other communications modalities such as orbiting earth satellites and cable television for their potential use in biomedical communications.

Clearly, more effective communication among the world's scientists and health care practitioners will lead to better research with minimal duplication of effort; it will permit a narrowing of the gap between the generation of new knowledge in the laboratory and the application of that knowledge to the treatment and prevention of illness.

Biomedical Communications Research and Development

The NLM's primary research and development program is conducted by the Lister Hill National Center for Biomedical Communications. The communications media which promise to have the most impact on the health environment in the next decade are satellite, wireline, microwave broadband, and cable television networks. The Lister Hill Center is conducting development programs and/or supporting pilot projects in each of these areas. In addition, it is exploring the use of computers for medical simulation and education.

For several years the Center has supported an experimental voice network linking over 20 Alaskan native villages with medical centers capable of providing health care consultation. The network, based on a NASA Applications Technology Satellite (ATS-1), has demonstrated the benefits of improved voice communication for the health care of widely

*MEDLARS: Medical Literature Analysis and
Retrieval System.

dispersed populations. An evaluation of the project showed a four-fold increase in the number of patients being treated with a physician's advice since the experiment's inception. Further experiments are employing a recently-lunched communications satellite to study the effectiveness of live television for consultation between physician-based hospitals and two small, remote clinics in Alaska staffed by health aides. The satellite also permits a link-up of Alaskan native village clinics and Indian Health Service hospitals with the Indian Health Service information service in Arizona. Through this communications link, the clinics are able to obtain up-to-date medical records on all listed village residents.

After Alaskan villagers have been trained to operate the satellite ground terminals, experiments will evaluate the use of satellites to support medical education as well as health care in remote regions. Future plans envision the use of existing and projected NASA satellites to explore the full spectrum of benefits for medicine made possible by this new technology, particularly in regions which are relatively remote and sparsely settled.

Similarly, the Center has demonstrated the value of interactive television for providing continuing education and medical services in rural settings and is supporting the use of cable TV to provide health education and services to an elderly urban population.

The Center is actively engaged in developing the potential of computer-assisted instruction as one means of reducing the time and manpower needed to train health professionals. It is also planning for the establishment of a new medical simulation training laboratory.

Library Operations

The NLM collects materials exhaustively in roughly 40 biomedical areas and, to a lesser degree, in related subjects such as general chemistry, zoology, botany, and psychology. The holdings include approximately one and a half million books, journals, technical reports, documents, theses, pamphlets, microfilms, and pictorial and audiovisual materials. Also housed in the Library is one of the Nation's largest medical history collections, with contents dating from the 11th to the mid-19th century.

Selection and acquisition of materials for the NLM collection is only the first step. To be useful, the information must be organized and made accessible to those who need it. The NLM conducts a continuous program of indexing the information contained in the world's major biomedical journals. Since 1964, this information has been entered into the NLM's computerized bibliographic storage and retrieval system, MEDLARS. The MEDLARS data base is used for the computerized publication of Index Medicus, a monthly index to the world's important biomedical journal literature. MEDLARS also is used to produce a number of specialized bibliographies and individual demand searches on specific topics. Since 1971, the utility of the MEDLARS data base has been greatly augmented by the advent of MEDLINE. This provides direct access to the data stored in the NLM computer through remote computer terminals located throughout the United States and at points abroad. With MEDLINE, individuals at libraries thousands of miles from Bethesda can "converse" with the NLM computer to retrieve precisely the bibliographic citations which they need--in a matter of minutes.

MEDLINE is currently being augmented by the incorporation of author abstracts of the literature into the system, thus providing much more explicit bibliographic information on the approximately two million citations available in the data base. Plans also call for the development of a system permitting free-text searching, which would eventually enable users to query the data base directly for explicit information not generally available in a controlled vocabulary. It will also allow use of the system with much less training than is presently required.

The NLM has developed other on-line systems to assist in the efficient dissemination of cataloging and serials information. Plans call for the development of a management information system using these data bases for network-controlled document delivery fully integrated with the bibliographic retrieval system. Such an arrangement would eventually permit automatic routing of requests to the most appropriate libraries concerned. It would also make possible access to the network by many hundreds of small libraries with teletypewriter equipment, thereby greatly stimulating efficient sharing of resources on a national level.

Medical Library Assistance

Through its programs of medical library assistance, the NLM provides grants for training, research, special scientific projects, publications, and medical library resources, and contracts for a national network of Regional Medical Libraries (RML).

Emphasis in the training program is now being placed on producing specialists who can integrate computer technology into all phases of clinical medicine--teaching, practice, and research. Research grants are intended to help medical libraries find more efficient means of meeting the biomedical information needs of the clinical, research, and academic communities which they serve. Projects currently being supported include a study of how best to utilize computer information banks in support of patient care and research. Resource grants support the establishment, expansion, and improvement of the basic collections and services of medical libraries. With this assistance, for example, a small hospital library can purchase a core collection of monographs and journals most frequently needed by local health practitioners. This permits the small local library to meet the bulk of its users' information needs without the delays involved in relying on a larger, more distant facility. In those instances where the local library does not have the material requested, it can call on the nearest RML. By helping to support a network of such RML's covering the entire nation, the NLM guarantees smaller libraries access to the large mass of material which it would be wasteful, if not impossible, for them to maintain in their own collections. Services provided by the RML's include document delivery, reference assistance, and continuing education of medical librarians. Approximately one and a half million interlibrary loans are made annually by the RML network. The cost is shared among the users, state and local agencies, and the NLM.

Audiovisual Programs

The National Medical Audiovisual Center (NMAC), located in Atlanta, Georgia, administers programs to improve the quality and facilitate the use of biomedical audiovisuals in support of health care and education. Concentrating on instructional use of media and systems and on their utility in improving the educational process, NMAC is the focus of NLM efforts to provide access to audiovisuals for the biomedical community. The Center closely coordinates its work with that of the Bureau of Health Resources Development, HRA, to enhance educational efficiency, encourage educational innovation, and ensure equality of access to training in schools of the health professions. NMAC also seeks the advice of and cooperates with major national health professional organizations to ensure that the Center focuses on the areas of most need to the biomedical community.

Toxicology Information Program

The Toxicology Information Program (TIP) serves as the national focal point for information on toxicology. It supports organized toxicological information activities, encourages communication within the toxicological community, and provides services and publications which make information available as needed to toxicologists and health professionals.

TIP is in the process of creating automated toxicology data banks from the biomedical literature and files of collaborating government agencies, universities and industry. TIP provides computerized toxicology information and data services for the scientific community through query response services, publications, and operation of on-line information retrieval systems such as TOXLINE.

TOXLINE usage is expected to reach approximately 8,000-10,000 hours this year, representing 30,000 to 45,000 individual searches. The bibliographic file will reach a level of 450,000 entries, with records from "specialty" literature files selected to enrich TOXLINE in key subject areas. CHEMLINE, a new on-line retrieval system for chemical nomenclature information, also will be expanded.

A products composition file containing information on approximately 19,000 commercial products will be made available for users. In addition, a major effort will be undertaken to construct a toxicology data bank containing over 500 compounds and data elements.

Next year, TOXLINE system usage will reach an estimated 75,000 to 90,000 individual searches. The Office of the Assistant Secretary for Health has assigned responsibility to TIP for the coordination of all toxicology information activities of DHEW. Support will be directed to a series of projects to the needs of agencies dealing with toxicological information and data.

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND STROKE

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NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND STROKE

Introduction

The National Institute of Neurological Diseases and Stroke (NINDS) conducts and supports research relating to the normal functioning of the brain, nerves, muscles and sense organs, and to the cause, diagnosis, therapy and prevention of many disorders. These include cerebral palsy, epilepsy, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, muscular dystrophy, myasthenia gravis, stroke, head injury, spinal cord injury, and many disorders of hearing and speech.

The Institute carries out its research responsibilities through an extramural program, which administers grants and contracts for projects at non-Federal academic and other institutions, and an intramural program at Bethesda consisting of basic research laboratories and clinical units. Grants are of several types: individual research grants, and both clinical research center grants and research program-project grants which are usually multidisciplinary attacks on specific diseases of national concern, such as stroke and spinal cord injury. Hundreds of the supported studies relate to the basic sciences which add to the store of knowledge essential to the conquest of neurological diseases.

NINDS training grants have been instrumental in helping to develop specialists needed to expand the scope of investigations in the neurological field and to apply new knowledge to the treatment of disease. The Institute also provides strong support for the development of research facilities at universities and other research institutions to permit further expansion of research and training resources.

Interaction between the Institute's own scientists and the scientific community, both here and abroad, is increasingly important. This relationship gives added strength to the Institute's four major program areas: neurological disorders research, stroke and nervous system trauma research, communicative disorders research, and fundamental neurosciences research. These programs are described in detail in the sections that follow.

Neurological Disorders Research

In the overall NINDS program structure, the entire spectrum of neurological disorders other than stroke and trauma is grouped in the general category called neurological disorders. This category includes epilepsy, the neuromuscular and sclerosing diseases, parkinsonism and other degenerative diseases of later life, infectious disorders of the nervous system, tumors of the nervous system, and neurological diseases of childhood, including cerebral palsy. These ailments together account for a major fraction of the suffering and economic loss caused by all of the neurological and related diseases.

Chronic Neurological Disorders of Childhood

Many neurological and communicative disorders result from damage to the developing nervous system before, during, or after birth. Some of these are genetic in origin, or may involve metabolic deficiencies. All require major investments of both medical and social services, and exact a toll in personal anguish that cannot be measured.

Since 1959 NINDS has supported a long-term multidisciplinary study to learn much more about neurological disorders of early life. Called the Collaborative Perinatal Study, over 50,000 mothers and babies have been studied at 12 medical institutions since 1959. Much valuable data has been collected and much remains to be analyzed and published.

A recent and unexpected finding is that certain anomalies associated with high perinatal mortality do not influence development or mortality of those infants who survive. For example, although it is now well established that maternal smoking during pregnancy increases the risk of the baby's death, long-term effects of maternal smoking on growth and intellectual development in children who survived the perinatal period have not been identified by scientists studying the problem at one of the collaborating institutions.

Occurrence of a single umbilical artery is an example of a malformation known to result in high perinatal mortality, yet not adversely affecting development in surviving infants up to four years. From the results of this study, it now appears that with the exception of a higher incidence of hernias, there is no difference in the development or mortality between these infants and carefully matched infants used for controls.

Findings such as these make possible more accurate counseling of the parents of affected children. In the case of a child with a single umbilical artery, parents can now be assured that once the perinatal period has passed, the outlook is as good as for another without the defect.

The link between prematurity and cerebral palsy and other developmental disabilities is well known. Data from the Study also show that low-birth-weight infants constitute a disproportionately large share of those suffering perinatal death or later neurologic abnormalities including cerebral palsy. In addition, the data substantiate a relationship between birth weight and factors already known or suspected of influencing it. Separate NINDS studies document maternal weight gain as the most important of 32 factors influencing the weight of an infant at birth.

Because of the enormity of the Study, a massive amount of data is being analyzed. Some of these data are unique in their quality and completeness, their prospective nature, and in the safeguards which were imposed to assure comparability in their collection. They represent a national research resource for scientists investigating events of intrauterine and postnatal life that cause neurological handicaps.

Inherited Neurological Disorders

A number of advances in the treatment of hereditary metabolic diseases which affect the nervous system have been made by Institute scientists. In combined basic and clinical studies they succeeded in purifying the enzyme lacking in the organs and tissues of patients afflicted with Fabry's disease, one of several lipid storage diseases which can result in mental retardation and early death. By injecting the purified enzyme into the patients, these scientists were able to temporarily reverse the effects of the metabolic defect. Very recently, another lipid storage disease, Gaucher's disease, has been successfully treated by injections of the enzyme that is missing in the disorder. In the latter case improvement has persisted for over six months following the enzyme replacement therapy.

Another accomplishment of the past year was documentation of the reliability of the prenatal diagnosis of Gaucher's disease by enzyme assays performed on cultured amniotic cells. This, coupled with demonstrations of the feasibility of the prenatal diagnosis of Fabry's disease and Tay-Sach's disease by amniocentesis (a procedure in which a needle is inserted into a pregnant woman's uterus to draw a small sample of amniotic-sac fluid) has made NINDS one of the country's most frequently consulted centers for genetic counseling.

Epilepsy

Epilepsy is the name given to a set of symptoms--called seizures--and to the underlying mechanisms which cause them. Precisely defined, epilepsy is "recurring, abnormal, uncontrolled electrical discharges of brain cells." Brief episodes of unconsciousness, uncontrolled movements, erratic behavior or combinations of all three are the manifestations.

In a recent report, the Epilepsy Foundation of America presents strong evidence that there are at least four million persons in the United States who have some form of epilepsy and that the total cost of their disabilities to the Nation may exceed $4 billion a year.

In about 60 percent of the known cases of the epilepsies, seizures are prevented by drugs, or in some instances, surgical treatment. In the other 40 percent, control of attacks is partial or absent.

To try to find causes, preventives and best treatments for the epilepsies, NINDS conducts and supports basic, clinical, pharmacological and surgical brain research. It also supports efforts to increase the percentage of completely controlled cases through development of new antiepilepsy drugs, scientific comparisons or the effectiveness of existing drugs, improved communications between researchers and public education.

The epilepsies are not contagious and there is only slight evidence that heredity is a factor. Most researchers agree that brain damage has something to do with causing epilepsy. Seizures often follow unusual birth trauma, severe drug or alcohol intoxication, head injury, fever and some infectious diseases. They can be caused in humans and experimental animals by surgical brain injuries or by certain chemical or electrical stimulation and are also associated with brain tumors, abscesses and congenital malformations. Because so little is known about causes, and effective treatments are not available for many, there is much need for continuing research.

The research tools of epilepsy are the electroencephalograph (EEG), telemetering-computer equipment, animal models, gas-liquid-chromatography (to measure levels of antiepilepsy drugs in patient's blood samples), surgery and drug therapy.

Drug therapy began in the 1850's with potassium bromide, progressed to phenobarbital by 1912 and was greatly improved with the introduction of diphenylhydantoin (Dilantin) in 1938. Phenobarbital and Dilantin are still the best drugs for effective and safe use in controlling seizure activity. Today there are 14 standard drugs marketed for epilepsy treatment in the United States. The 14th, carbamazepine (Tegretol), was added in August 1974, the first new drug for long-term use in epilepsy to be approved since 1960 when legislation first required that a drug's effectiveness as well as its safety must be proved before it can be approved by the Food and Drug Administration.

Five epilepsy research centers are supported by the Institute. They are at the University of California at Los Angeles, the University of Utah, the University of Washington at Seattle, the University of Wisconsin and the Yale University School of Medicine. These centers generate valuable knowledge about basic brain functions and continue developing useful new techniques for managing the epilepsies. In addition, there are over 100 Institute-supported, epilepsy-related projects in 14 states and five foreign countries.

Much of the Nation's antiepilepsy drug research efforts are conducted and supported by the Institute under the guidance of an NIH Advisory Committee on the Epilepsies composed of medical school, drug-industry, and Government representatives.

The Institute has also initiated the feasibility stage of a Comprehensive Epilepsy Program with three major objectives: to support clinical and appropriate laboratory research in diagnosis, treatment, prognosis and prevention of epilepsy; to train and educate physicians and other professionals in new advances in epilepsy research and treatment and establish a broad public education program; and to demonstrate to those with epilepsy the value of up-to-date preventive, medical and rehabilitative, psychological, vocational, educational, and social services. Objectives will be achieved by effectively coordinating epilepsy-related research, teaching, and health-care delivery services in a given geographical area and by extending existing services to speed applied research. Eleven feasibility studies are underway and it is expected that one or more Comprehensive Epilepsy Centers will be established under contract by mid-1975.

Research-generated knowledge is useful only to the degree that it is communicated to people who can use it. To aid scientists and professionals, the Institute has sponsored symposia, abstract services, books and monographs, and international exchange visits. For the layman, the Institute produces pamphlets, special reports, newspaper and magazine articles, health columns, radio and TV announcements, answers more than 75,000 requests annually for epilepsy information, and arranges TV appearances by Institute scientists.

Parkinson's Disease

In an effort to better understand the diseases that afflict the nervous system after age 60, the NINDS has focused research attention on Parkinson's disease. This is a progressive neurological disorder of unknown cause affecting certain brain areas involved in the control and regulation of movement. Its onset may be insidious and its progression almost imperceptible, but it is ultimately characterized by tremor, rigidity, bent posture, and other disabling symptoms.

The causes of Parkinson's disease are still unknown. Certain forms may result from a still undetected virus, and a few metallic poisons have been suspected. One theory on the cause is that coordinated muscle control depends upon a balance of two neurochemical systems, cholinergic and dopaminergic, and that the symptoms of parkinsonism are caused by overactivity or underactivity of one or the other of these systems.

Recent research has shown that depletion of substances in the brain, notably dopamine, accompanies parkinsonism. Although the question of how this depletion occurs has not been answered, the knowledge that it does occur has led to a new and highly effective form of replacement therapy. The therapy is based on a gradual buildup to large oral doses of the amino acid, levodihydroxyphenylalanine, abbreviated as L-Dopa or levodopa, which is the precursor of dopamine.

The NINDS program in parkinsonism consists of grant support for several large interdisciplinary research groups and some 20 smaller, more circumscribed research projects. Also, an intramural program in neuropharmacology, shared with the National Institute of Mental Health, is in progress.

Muscular and Neuromuscular Diseases

The neuromuscular disorders, characterized generally by weakness, wasting, and fatigue of the muscles, primarily affect children and young adults. The two most common disorders in this group, the muscular dystrophies and myasthenia gravis, afflict some 200,000 and 30,000

Americans respectively. When other less prevalent neuromuscular disorders are included, estimates of the number of Americans with these conditions range from 250,000 to as many as one million.

The Institute's laboratory studies on muscular dystrophy, myasthenia gravis, and other neuromuscular disorders are centered in its Medical Neurology Branch at Bethesda. Multidisciplinary research is aimed at evolving basic research techniques and applying them to clinical neurological problems.

The NINDS also supports 122 research projects related directly to neuromuscular disease in numerous hospitals, medical schools, and universities, including large program-project grants at the University of Pennsylvania and at Columbia University. The Institute has also supported a contract in the neuromuscular area at the Department of Neurology, Warsaw Medical Academy, Poland.

Muscular Dystrophy

In general, a patient with muscular dystrophy becomes weaker as muscles deteriorate. He may become confined to a wheelchair and later have difficulty with the ordinary activities of living. Death, however, is usually not caused directly by the disease but by an infection leading to respiratory failure or, in some cases, by heart failure when heart muscle becomes involved.

Historically, muscular dystrophy has been thought to be a muscle disorder, and most researchers have concentrated on this part of the motor unit, ignoring the motor nerve and the peripheral nerves which carry messages to the muscle fiber. However, failure of researchers to find the seat of disease in the muscle has led some investigators to look elsewhere along the motor unit. Some believe that the source of the problem may lie in the nerve, or that a single defect elsewhere might be affecting both the muscle and the nerve.

A new hypothesis of the cause of one form of muscular dystrophy developed by the NINDS Medical Neurology Branch proposes that the muscle damage in patients with the Duchenne type of progressive muscular dystrophy might be produced by abnormalities of the small blood vessels within the muscles, rather than by a primary defect in the muscle fiber itself.

Accurate diagnosis of the specific type of muscular dystrophy is vital since patients with other closely related neuromuscular diseases that simulate muscular dystrophy can be treated successfully, even though there is no treatment yet for many types of muscular dystrophy. In addition, accurate diagnosis facilitates evaluation of any treatment and aids the physician in his efforts to counsel the patient and his family.

The Muscular Dystrophy Associations of American, Inc., through a nationwide network of 130 clinics, offer differential diagnosis free to anyone suspected by his physician to be suffering from muscular dystrophy or related neuromuscular disorders.

Sophisticated methods developed through research are providing scientists with increasingly more detailed knowledge of the various muscular dystrophies and are leading to improved diagnosis. Diagnosis is usually based on the combination of clinical examination, family history, microscopic examination of muscle samples (biopsies), electromyography (recording of the muscle's electrical activity) and determination of levels of creatine phosphokinase (CPK) (the enzyme that leaks out of damaged muscle tissue) in the blood.

Recently NINDS grantees observed abnormally elevated protein synthesis in muscle tissues of patients with Duchenne muscular dystrophy. This finding has already spurred development by these investigators of a promising differential diagnostic test and a carrier identification test.

Myasthenia Gravis (MG)

MG is a chronic neuromuscular disease that generally appears between ages 15 to 35 years in females, and ages 40 to 70 in males. It is characterized by weakness and abnormally rapid fatigue of the voluntary muscles, with improvement following rest.

Formerly many MG patients died within the first few years of their illness but during the past two decades there have been significant reductions in the death rate and degree of illness, even in the most severe cases. Improvements in support systems, such as intensive hospital care, respirators and antibiotics, and widespread use of tracheostomy (surgery to open the windpipe) undoubtedly have contributed, but the main advances have been in the use of anticholinesterase drugs and adrenocorticotrophic hormone (ACTH). Although the cause of MG is still debated, and therapy is directed partly toward the treatment of symptoms, MG is one of the most successfully managed neuromuscular disorders. Today scientists believe the majority of patients will live out a normal lifespan, and an estimated three-fourths of moderately affected MG patients can lead virtually normal lives.

Basic research on the transmission of nerve impulses for muscle activation has produced an increasingly precise picture of this mechanism and has led to refinement in treatment. Several drugs provide relief from symptoms, and others may be effective against one or another cause. For nearly 40 years the anticholinesterases, especially pyridostigmine and neostigmine, have been mainstays of symptomatic treatment.

A new treatment introduced by NINDS intramural scientists--a high, single dose, alternate-day, oral prednisone regimen--has proven extremely beneficial over long periods in the majority of 20 patients. Prednisone is a synthetic drug whose action resembles the natural adrenocortical hormone, cortisone. Patients over age 40, especially males, respond best. Physicians throughout the world have confirmed the beneficial results. The NINDS scientists now consider alternate-day prednisone the most effective treatment and believe it may suppress the disease sufficiently long for it to disappear.

Despite therapeutic success, the cause of MG is still unknown, but an immunological mechanism has long been suspected. The role of the thymus in the body's immune mechanisms and its close association with MG is a major clue in this theory.

Thymectomy (surgical removal of the thymus gland) proved beneficial in 89 percent of a large series of patients, most of whom were severely affected, NINDS-supported scientists recently reported. Significant improvement also was reported in a long-term study of the surgery in juvenile patients, and other studies indicate that benefits may be enhanced with irradiation of the thymus before the surgery. Some scientists now believe that thymectomy should be performed routinely on all MG patients, especially the younger females.

Sclerosing Disorders and Slow Virus Infections

Multiple Sclerosis

Multiple sclerosis is a neurological disease of the 20-40 age group for which no effective treatment is available. An estimated 250,000 Americans are afflicted with this disease, plus many more with other sclerosing disorders such as amyotrophic lateral sclerosis, spinal muscular atrophy, and allergic encephalitis. The elucidation of multiple sclerosis presents one of the urgent problems of basic neurology.

The cause of multiple sclerosis remains unknown despite the compiling of enormous amounts of information from basic research, clinical studies, and epidemiologic investigations. The neurological symptoms of multiple sclerosis in part are a result of the patchy destruction of myelin. When the myelin sheath surrounding a nerve fiber breaks down, the conduction of impulses along the now exposed fiber is disrupted. Eventually scar tissue forms in the demyelinated areas, producing the sclerotic plaques for which the diseases is named.

There is no treatment for multiple sclerosis that provides any significant, lasting benefit. From time to time new treatments have been reported helpful, but when tested have not proven effective. An example is ACTH (adrenocorticotrophic hormone). The final report of a five-year collaborative study supported by the NINDS on ACTH indicates that this agent is slightly beneficial during the first few weeks of treatment, but there is no evidence that the drug is effective for long-term use. The spontaneous episodes of exacerbation (increase in symptoms) and remission seen in multiple sclerosis make an evaluation of a particular therapy very difficult.

It is now believed that many patients may live up to 70 percent or more of their normal lifespan. Early death is usually the result of complicating infections of the lungs or bladder.

Multiple sclerosis exacts a very heavy annual toll of disability, striking its victims mainly in the most productive period of their early adult lives. The estimated cost of patient care in the United States alone is at least $250 million each year. Additional millions are lost to patients and to society as a consequence of jobs lost or the inability of stricken housewives and mothers to function.

In October 1972, Congress enacted a public law establishing the National Advisory Commission on Multiple Sclerosis to determine the most effective means of finding the cause of and cures and treatments for multiple sclerosis. The Commission presented its report to the Secretary (HEW) in February 1974. Since that time NINDS has been implementing a number of the recommendations.

The Commission recommended that the Institute underwrite major programs in virological research, and promote major research into immune mechanisms. The Institute has had a strong virological research program which it is expanding. Recently, two contracts dealing with physical and biochemical methods for study of multiple sclerosis tissues for viruses, biochemical changes, and immunological reactions have been awarded. At the Institute's Bethesda laboratories, a new laboratory of neuro-immunology is being established and should be operative by January 1975. Special training and fellowship programs in neuro-immunology and neuro-virology also have been inaugurated.

Of the major research approaches to multiple sclerosis, epidemiology of the disease was one of the first to be extensively investigated. Multiple sclerosis is most prevalent in the world's temperate zones; it is less prevalent in warm regions. Consequently, investigators have long sought the cause of multiple sclerosis in some factor related to geography.

The Commission recommended various epidemiological studies of the disease. Two contracts have now been negotiated. One of these relates to the Shetland-Orkney Islands where the prevalence of multiple sclerosis is at least 200 per 100,000 which is two and one-half to three times higher than the rates in any other known population. Institute scientists believe that a thorough epidemiological survey of these island groups may reveal conditions which predispose the population to the extraordinary high rate. The second contract involves a nationwide survey of the prevalence and cost of multiple sclerosis.

Studies in Israel, Hawaii, South Africa and the United States indicate that multiple sclerosis is probably acquired before adolescence and that the critical exposure period may be prior to 15 years of age. Individuals migrating from a high to a low multiple sclerosis risk area after about age 15 seem to carry their "high risk" with them, whereas individuals migrating before this age show a low rate of multiple sclerosis, like the native population in the low risk area.

The patterns of age and geography coming from these and other epidemiologic studies have led many scientists to conclude that some infectious agent is involved in initiating the disease.

Because multiple sclerosis is a disorder of unknown etiology (cause), much of the research remains at the basic level at which the fundamental mechanisms of the disease can be elucidated. In addition to basic research, a large patient study of immunological, virological, and neurochemical aspects relevant to demyelinating disease is now being conducted at the new Reed Neurological Research Center at the University of California at Los Angeles.

Recently, the NINDS joined the National Multiple Sclerosis Society in providing a grant to the Wistar Institute and the University of Pennsylvania School of Medicine for nearly $2.5 million over the next three years to support the most intensive collaborative study of multiple sclerosis ever made. The project is specifically designed to determine the etiology and pathogenesis (course) of multiple sclerosis, with emphasis on the virologic and immunologic aspects. As suggested by the National Advisory Commission, an additional multiple sclerosis clinical research center has been funded at Emory University, Atlanta.

Amyotrophic Lateral Sclerosis (ALS).

ALS is a relatively uncommon neurological disorder of unknown etiology with an incidence of 8,000 to 10,000 patients in the United States. It occurs most often in males of middle age or older. It is characterized initially by muscle weakness and wasting brought about by degeneration of motor cells in the brain and spinal cord. At the present time treatment is symptomatic. The average course of ALS is about three to four years from the appearance of symptoms until death, but some individuals remain active for 10, 15 or more years, with long periods of little or no progress of the disease.

The Institute's ALS research includes a long-term extensive program on Guam where a form of ALS has been found to have an incidence of 20 times the rate in the United States. On Guam and on the Kii Peninsula in Japan, where a high incidence of ALS has also been found, the Institute has developed studies aimed at elucidating which environmental factors might be responsible for the disproportionate number of ALS cases in these areas. A small research facility is maintained on Guam for these studies.

Slow Viruses

The pioneering studies of NINDS scientists on kuru, the fatal dementia found the New Guinea Aborigines, has focused world attention on the role of slow and latent viruses in causing chronic degenerative diseases of the central nervous system. The transmissibility of kuru from human brain samples to chimpanzees and other primates, and from primates to primates, with incubation periods of as long as eight years clearly established that the disease is caused by an infectious agent of viral dimensions but very unusual properties. In addition to the long incubation period, the agent exhibited resistance to such standard virus-incubating procedures as heat, formaldehyde and ultraviolet radiation.

In these properties it resembles two animal slow virus diseases, scrapie (of sheep and rodents) and transmissible mink encephalopathy. Each attacks the brain to produce a fatal spongiform encephalopathy, characterized by a major destruction of nerve cells that accounts for the dementia seen in terminal kuru patients.

Because another rare but widely distributed encephalopathy of man, Creutzfeldt-Jakob disease, has a similar clinical picture, NINDS scientists tested its transmissibility from human brain samples to primates. Like kuru it proved to be transmissible after similarly long incubation periods. Since this striking observation, two cases of presumed accidental transmission from man to man have been recorded, one to a neurosurgeon operating on an infected patient and one to a recipient of a corneal transplant from a donor who subsequently developed Creutzfeldt-Jakob disease.

NINDS scientists believe that these four slow virus diseases are closely related virologically and that the agent may in fact be identical except for modifications in the host brain. A supporting clue seems to be provided by the epidemiological study of a cluster of Creutzfeldt-Jakob cases in Isreal, all of whom proved to be Libyan Jews accustomed to eating partially cooked sheep brains. Both NINDS intramural and grant-supported scientists are vigorously pursuing the characterization of these agents, using scrapie in mice as the experimental model. So far these agents exhibit none of the viral immunological characteristics that would permit a more rapid investigation. Hence immunologists and virologists face a real challenge since they must still resort to the cumbersome and expensive procedure of mass intracerebral inoculations of animals to screen for the infectious agents.

Two other discoveries by NINDS intramural and grant-supported scientists have considerably widened the slow virus horizon. One is the demonstration that a rare consequence of early childhood infection with the common measles virus is the development about six years later of a fatal demyelinating disorder, subacute sclerosing panencephalitis (SSPE). Antibodies to measles virus are exceptionally high in cerebrospinal fluid and brain of afflicted patients and recovery of the latent or hidden virus has been demonstrated. Evidence is accummulating to implicate a blocking factor in the blood serum of these patients which prevents access of lymphocytes, the body's source of antibodies, to the infected cells. A major effort is under way to elucidate the nature of the blocking factor and its precise mechanism of action. Not only may such studies provide prevention or treatment of SSPE but they may also uncover a general principle that could explain many other latent virus disorders.

Another rare and fatal demyelinating disease of the human brain is progressive multifocal leukoencephalopathy (PML), which NINDS grantee scientists have shown is caused by viruses of the papova virus group. This is a startling finding because this group of viruses has classically been considered to be oncogenic (tumor-producing) viruses. And indeed viruses isolated from the brains of patients dying of PML prove to be potent tumor producers when inoculated into experimental animals.

In SSPE and PML the basic problems appear to be disorders of cellular immunity within the central nervous system. The whole field of neuroimmunology is relatively recent, so that the Institute has given top priority to the training of additional personnel in this field and has created a laboratory within its intramural program to complement the strong slow virus team already at work.

The examples of slow and latent virus neurological diseases are likely to be only the forefront of a great many more. Alzheimer's and Pick's diseases are good candidates for a slow virus etiology, and both multiple sclerosis and amyotrophic lateral sclerosis are generally considered to represent latent virus and/or autoimmune diseases. The Institute anticipates more major breakthroughs in these areas of research and has set its priorities and mobilized its resources accordingly.

Stroke and Nervous System Trauma Research

This Institute program area is focused on stroke, spinal cord injury, and head injury. A common goal of research on all three of these disorders is the protection of the brain or cord during the acute phase of trauma in order to preserve as much of the viability and function of nerve cells as possible. New non-invasive procedures have been developed to diagnose and monitor such problems. Of particular promise are new scanning instruments utilizing X-rays combined with computers to detect differences in nerve tissue density which reflect edema (excess fluid) and ischemia (decreased blood supply). The scanners are being applied to stroke and nervous system trauma at several NINDS-supported centers and one will shortly be in use at the NIH Clinical Center.

Stroke

Stroke is the third largest cause of death and a leading cause of long-term disability in the United States. Each year about

500,000 Americans are stricken, and about 200,000 die. There are about 2 million stroke survivors in the country, with varying degrees of disability. Last year an NINDS-sponsored Commission on Stroke estimated that 30 percent of stroke survivors recover sufficiently to return to work or to their normal activities; 55 percent have their lives impaired, but are able to carry on the activities of daily living, often with help; and 15 percent become completely incapacitated and are so helpless that total nursing care is required for the rest of their lives.

A stroke is a sudden loss of brain function resulting from interference with the blood supply to the brain. It is often the culmination of progressive cerebrovascular disease, which may extend over many years, and which may not be readily detectable. Some strokes are minor episodes, while others may cause death in a few minutes. Usually they are brought on by one of four events: thrombosis--a clot within a blood vessel of the brain or neck; cerebral embolism--the blocking of a blood vessel in the brain by a piece of clot or other material carried through the circulation from some other part of the body; narrowing (stenosis) of an artery supplying blood to the brain; or cerebral hemorrhage--the rupture of a cerebral blood vessel with bleeding into the brain tissue.

An important underlying cause of cerebrovascular disease is atherosclerosis. High blood pressure (hypertension) has also been shown to be associated with a considerable increase in the frequency and severity of vascular diseases of the brain, especially cerebral hemorrhage. Among other causes of stroke are aneurysms, and abnormalities in the clotting process.

In the past 10 years there has been substantial increase in scientific and medical interest in cerebrovascular disease, brought about, in large part, by the growth of the NINDS stroke program. In Fiscal Year 1973, the Institute supported 37 research project grants, 15 clinical research centers, and 10 acute care research units. Additional support was provided for training in neurology and other related disciplines, as well as through support of meetings and publications.

Cerebrovascular clinical research centers, located in large university medical complexes throughout the country, now make up the largest segment of the program. These units, most of which are multidisciplinary, are staffed by as many as 15 to 20 scientists and physicians, plus technicians and other assistants. They vary in approach, some concentrating on single research areas, such as the epidemiological aspects of stroke, or research on aphasia. Other centers are broader in focus, often working with several approaches. Generally the centers have interrelated clinical and basic research programs, and have accommodations for up to 30 research patients. All of them also conduct training programs for young physicians, scientists, and other staff members.

A new program to provide funding for Acute Care Research Units was launched in March 1973. These units are being equipped for precise monitoring of vital signs and levels of body function, and will strive to find ways of preventing small strokes as well as treating the acute phases of major strokes.

A new diagnostic technique, computerized soft tissue tomography, has been hailed by a prominent radiologist as "probably the most important advance in radiology in 50 years." The technique, embodied in a scanning instrument, employs a narrow beam of X-rays to rapidly scan the patient's head in a series of thin slices. The beams pass through the head and hit two crystal detectors which feed signals into a high speed computer. At each of 28,000 points along the scan, the computer calculates the difference between the X-rays originally emitted and those received. The computer also produces an oscilloscope picture for immediate viewing or photographic recording. Two patients per hour can be scanned. The equipment is sensitive enough to detect differences in absorption of only one digit in a scale from -500 (air) to +400 (bone), and has so far been used to find cysts, neoplasms. abscesses, cerebral infarcts, intracerebral hemorrhages, and even plaques of multiple sclerosis. It is considered to be 100 times more sensitive than conventional X-ray diagnosis, and may well make the older methods obsolete, especially the "invasive" ones which involve injection into the body of dye, radioisotopes, or air.

Spinal Cord Injury

Spinal cord injury can result in paraplegia, quadriplegia, or partial paralysis. In terms of human suffering and economic loss, severe injury to the spinal cord is one of the most devastating of all personal tragedies because once destruction to the spinal cord has occurred, nothing now known can reverse the effects of the injury.

It is estimated that there are 125,000 paraplegic and quadriplegic patients in the United States today, and that there are 10,000 to 12,000 new civilian paraplegics each year. Four out of five victims are males between the ages of 15 and 25 who are injured in vehicle, sporting or industrial accidents or as a result of gunshot wounds or falls. Because of their youth at the time of injury, many victims spend as much as a half century in bed or wheelchair, without conscious sensation from the waist down. The cost of initial hospitalization and lifetime care of the spinal cord injured plus indirect costs in terms of lost earning capacity for the individual and reduced productivity for the Nation total billions of dollars each year.

In its search for ways to deal effectively with the problem of paraplegia, the National Institute of Neurological Diseases and Stroke has developed approches to four major areas of concern: acute injury, nerve growth and regeneration, neural prostheses, and arteriography.

Conventional thinking has been that spinal function is immediately and permanently lost following traumatic disruption of the cord. However, many years of NINDS-supported laboratory studies with experimental spinal cord trauma conducted by the NINDS and by universities and medical centers throughout the world now suggest that even severe physical injury does not always destroy the spinal cord. In some cases not all of the tissue damage may be directly related to the trauma, but may be an indirect result of it. Today, many scientists believe that the injury initiates a process of edema, vascular stasis and necrosis that eventually does destroy the cord. Within a definite time lag before this process is fully developed, the long fiber pathways are mostly intact. This raises the possibility that if this response of the tissue to injury could be stopped in the acute stage, then useful spinal cord function could be preserved and paralysis prevented.

To take advantage of these developments and to stimulate increased related research, the NINDS has established a targeted program on acute spinal cord injury. Through its extramural programs, the Institute is supporting five Acute Spinal Cord Injury Clinical Research Centers at: Ohio State University, Columbus; Yale University, New Haven, Connecticut; St. Joseph's Hospital and Medical Center, Phoenix, Arizona; The Medical University of South Carolina at Charleston; and New York University, New York City; and a large program project at the University of North Carolina at Chapel Hill. Additionally, there are three other targeted research programs on acute spinal cord injury at Washington University, St. Louis, Missouri; Hahnemann Medical College and Hospital in Philadelphia, Pennsylvania and the University of North Carolina at Chapel Hill.

Restoration of function in paraplegia is one of the Nation's greatest medical challenges. It is also an extraordinarily difficult problem because it involves both the regeneration of interrupted spinal cord fibers and their re-establishment of functional connections. Scientists know that two kinds of regeneration occur following injury to the central nervous system: (1) terminal regeneration, in which an injured peripheral nerve simply regrows its severed nerve process and (2) collateral regeneration, in which normal intact central nerve fibers in the region of denervated nerve cells sprout additional outgrowths which may reinnervate the adjacent denervated cells and thereby function in place of the lost neurons.

The neural prosthesis or electrical "by pass" approach to the problem of paraplegia is being actively pursued by the NINDS. Scientists are studying the nerve cells in the brain and spinal cord which control the muscles of the body with the specific aim of effectively "by passing" breaks in the spinal cord. The NINDS also monitors a contract program for developing prostheses for the neurologically handicapped, including paraplegics. Two such contracts at the University of California at San Francisco and Duke University, Durham, North Carolina, were recently initiated to develop a neuroprosthetic device for bladder control, and preliminary results appear to be quite promising.

Head Injury

Three million Americans sustain injuries to the head annually; 50,000 die from trauma to the brain, the majority being caused by traffic accidents. An estimated 250,000 citizens are permanently disabled each year. In contrast to stroke, morbidity rates from head injury are lower, but affect a younger population--students, wage earners, homemakers. The life expectancy for disabled survivors is therefore many years longer, and the economic cost to the Nation has been estimated at $1.5 billion annually.

Research in head injury is a major interest of the NINDS, which is currently supporting five Head Injury Research Centers, 13 related research projects, and a small intramural program at the NIH Clinical Center. These studies receive input from a variety of disciplines, including neurosurgery, neurophysicology, neuropathology, anesthesiology, nuclear medicine, and biomedical engineering. At present the program is oriented toward solving the more fundamental neurologic problems in head injury rather than those of logistics, safety, and similar concerns.

Communicative Disorders Research

More than 20 million Americans are afflicted with hearing, speech or language problems. Included in this figure are an estimated 14 million persons with a handicapping communication impairment, of whom some 2 million are totally deaf; approximately 2 million persons with an impaired ability to comprehend language; and about 10 million persons with speech disorders.

The communication process may be hindered by a multitude of problems including poor amplification of the message or interference with interpreting the incoming messages, storing the information, or generating meaningful language. Speech disorders may result from problems with any of the structures producing speech, such as the larynx, palate and mouth. Problems also can originate from emotional problems, poor muscle coordination, deafness, or language disorders.

NINDS is studying, through grants and at the newly created laboratory of neuro-otolaryngology in Bethesda, the prevention of communication disorders through an understanding of the biological functions involved. Concurrently, the Institute is supporting clinical studies on improved treatment.

An NINDS section on communicative disorders, working largely through contracts, is expanding its directed research to new problem areas, particularly those which do not receive funding from other Federal agencies. These areas include improved objective identification of young hearing-impaired children; improved measurement, treatment and prevention of speech and language disorders among adults who have experienced stroke or head trauma; effects of noise on children; noise and speech communication; and improved assessment and treatment of language communicative disorders not apparently attributable to sensory impairments. The section is currently supporting research on utilizing wearable master hearing aids and a study of the extent to which deaf persons are able to intergrate information obtained by lip reading with additional information derived from an electronic analysis of the acoustic speech wave form.

Hearing Disorders

Recent studies indicate that approximately 40 percent of deafness present at birth is hereditary. More than 60 types have been identified, most of them resulting from faults in five or six genes. Better understanding of hereditary deafness can aid counseling of prospective parents.

Another 10 percent of congenital deafness has resulted from prenatal rubella infection. The unique data collected from the NINDS collaborative perinatal study of more than 50,000 women and their offspring which was in progress during the rubella pandemic of 1964 have provided unique information on the correlation of rubella infection and deafness. The recent rubella vaccine has sharply reduced the incidence of rubella-associated defects in infants.

This information, plus recent advances in virology techniques, can now bolster understanding of the effects of a maternal virus infection on the fetus. Learning how other viruses are implicated in congenital deafness should be of help in improving methods of prevention.

Until hearing loss and deafness can be prevented, the early identification of infants born with hearing problems is vital as these problems can best be managed when they are discovered early. Recently, and NINDS grantee at Stanford University has introduced a computerized method of monitoring and detecting infants who are unresponsive to acoustic stimuli.

Certain drugs have been found to be toxic to the ear. During the past several years, the toxic doses and site of injury were defined, some by NINDS grantees, for dihydrostreptomycin, neomycin, kanamycin and ethacrynic acid.

Another contributing factor to hearing loss is noise. At present, the only method of dealing with hearing loss resulting from excessive noise is prevention. Research supported by NINDS at a number of universities and research centers is providing an understanding of the basic physiological structures and functions that are adversely affected by exposure to noise.

Hearing loss accompanying the aging process remains a problem of increasing prevalence accompanying the general aging of the population. A more thorough understanding of auditory anatomy and physiology may provide clues to understanding this problem and alleviating its effects.

Otosclerosis is the most dramatically treatable hearing disorder. It occurs when growth of spongy bone in the middle ear immobilizes a small ear bone, the stapes. This normally vibrates and conducts sound to the inner ear. Removal and replacement of the stapes has been reported to be effective in more than 90 percent of patients. The procedure has become increasingly safe with development of refined microsurgical techniques.

Another major and usually treatable disorder is otitis media, an inflammation of the middle ear space resulting from infection in the nose or nasopharynx. It responds to antimicrobial agents, surgery, and aural or topical decongestants.

The leading form of deafness is sensori-neural. This occurs when sound waves cannot be properly converted into a message which can be passed on to the brain. In addition to studying methods of prevention, scientists are determining whether improved hearing aids, including implantable ones, can be developed to help a person with sensori-neural loss.

While auditory prosthesis research still faces difficult obstacles, research on improving existing aids for the hard of hearing is helping increase the quality and the wearer's efficiency in using residual hearing. This year the Institute has had developed, under contract, a master hearing aid which will enable scientists to determine methods for tailoring hearing aids to be of greatest aid to the individual wearers. Research on improving fidelity, increasing ruggedness, and reducing distortion would increase hearing aid efficiency.

There has been some success in treating several other conditions causing hearing loss. Surgery for acoustic neuroma can dramatically prevent not only hearing loss but even death. Safe removal of these tumors growing on the sheath covering the acoustic nerve is possible because of striking advances in methods of early diagnosis and excellent microsurgical techniques.

Surgery is also being used, though sparingly, for some persons with Meniere's disease. This disorder, characterized by hearing loss, tinnitus (ringing in the ears) and vertigo, often will respond to medical measures including diet regulation, control of allergies, and drugs for treating the symptoms. In some persons for whom these measures are not adequate, cryosurgery and ultrasound are occasionally used in the inner ear, destroying the end organ of balance, the vestibule, but preserving cochlear (hearing) function. However, even when surgery is performed, symptoms often recur with a slow progression of hearing loss.

Speech and Language Disorders

Normally, speech activity originates and is organized in the brain's cerebral cortex. Information flows out through particular nerve tracts to the muscles involved in producing speech. There is then a sensory flow back to the central nervous system, probably indicating the position of all the structures related to speech, allowing other brain centers to project the necessary nerve impulses for a smooth flow of motor activity. An interruption in this process often accompanies neurological disorders such as cerebral palsy, stroke, multiple sclerosis, Parkinson's disease, dystonia and many others. Research is providing some understanding of speech problems caused by these disorders, such as the use of lateral cineradiography (X-ray motion pictures) to describe the nature of disturbed tongue movements during swallowing and speech.

Speech disorders also arise as a consequence of laryngectomy operations for cancer of the larynx which strikes approximately 6,000 persons each year. Dramatic advances have been made in maintaining or restoring speech function following surgery for removal of the larynx which contains the vocal cords. Improved methods of detection are enabling doctors to make earlier diagnoses, before the damage is too widespread. In these cases, conservation surgery is being used--that is, removing only the cancerous parts of the larynx, which provides the best prognosis for a functioning larynx. Following recent approval by the Food and Drug Administration of using teflon (suspended in glycerin) for injections to strengthen remaining tissue, restoration of normal speech and the ability to swallow have been made possible in a large percentage of patients.

An exciting advance in larynx surgery this year was made by scientists in Massachusetts. A carbon dioxide laser integrated with an operating microscope was used to selectively evaporate predetermined amounts of abnormal vocal cord tissue through a laryngoscope. Removal was reported to be precise and rapid. Follow-up examinations indicated normal healing similar to that in clean surgical wounds.

Disorders affecting language development can be present from birth, often the result of deafness, vocal paralysis, mental subnormality, early infantile autism and specific brain damage. Other children who do not suffer from any of these problems but still fail to develop normal language often have what is known as developmental dysphasia.

Language problems also involve children and adults as a result of brain trauma or stroke. Their condition is usually diganosed as aphasia, the inability to either assign meaning to words, repeat them or organize words into thoughts. Approaches to language rehabilitation generally follow one of four procedures. They may be based on: language structure (building up to increased levels of structural complexity); language acquisition of the normal child; perception and cognition (subordinating concern for linguistic structures); and stimulus-response combinations. More research is needed to develop methods for testing and measuring language disorders, to determine the nature of the disturbances, and to devise more effective treatment and rehabilitation.

Fundamental Neurosciences Research

The diseases of the human nervous system are among the most chronic, debilitating, costly and least understood of all those that afflict man. Suport in the neurosciences represents the investment by NINDS in the problem areas and at the frontiers of research on how the normal functioning of the nervous system is altered in the various neurological diseases. From hospital bedside to laboratory bench the investment comprises a collaborative continuum of clinicians and neuroscientists for whom these problem areas and frontiers represent some of the most challenging and perplexing that confront any group of biomedical investigators, because of that unique and most complex entity, the human nervous system.

The human nervous system, unlike other bodily organs cannot be replaced or substituted for. Unlike all other cells in the body, the principal cell of the nervous system, the neuron, cannot reproduce itself. At birth persons possess their fixed complement of neurons. Any losses are irreplaceable; the original allottment must last a lifetime.

From the brain and spinal cord the nervous system impinges upon every part of the body to initiate or regulate virtually all bodily activities and to receive back and respond to information on the status of those activities. Thus, the nervous system functions as a chemically-mediated communications system.

Hence the neuroscientist faces a variety of formidable difficulties in attempting to elucidate the mechanism responsible for normal functioning and to understand the nature of its derangements. Few of the fundamental studies can be done directly on the human central nervous system. The use of exotic species and the development of highly sophisticated specialized techniques are often the rule rather than the exception. Hence, most of the fundamental knowledge about the mechanisms by which a nerve conducts impulses have derived from studies on the giant axon (nerve) of the squid and required the development of the voltage-clamp and other techniques which have provided the major biological tools for electrophysiological studies on the nervous system, contributions made in large measure by NINDS intramural scientists.

The elucidation of how cellular energy is transformed into the transport of sodium and potassium across neural membranes to support nerve impulse conduction has been especially advanced by studies of the responsible enzyme system isolated from the electric organs of the Amazonian electric eel.

Microelectrodes, whose tip diameters are of the order of one micrometer (0.00004 inch) have been perfected to record the microcurrents developed by single nerve cells. These delicate instruments also have been used to apply specific chemicals or drugs to single cells while simultaneously recording their effects on cellular activity. The activities of single epileptic nerve cells have been monitored.

Other basic research programs have already been discussed in some detail in the test on inherited neurological disorders and slow viruses.

The focus on basic research at NINDS continues to be essential to the solution of a number of important problems of how normal functioning of the human nervous system is altered in neurological diseases and how such knowledge can be applied to their prevention, alleviation, or cure.

The foregoing account of the nature and significance of the NINDS investment in the neurosciences is necessarily incomplete. In fact neurosciences must be considered a continuum from the realm of human behavior and the patient's bedside to the most fundamental question of the biology of a slow virus or the molecular nature of a membrane receptor. The most elementary problem of Neurology, the conduction of nerve impulses, seem to be slowly yielding under the applications of increasingly powerful concepts and techniques. On the other hand the neuroscientist is the constant collaborator of the clinical neurologist because the ultimate solutions and the ultimate challenges are in the human central nervous system.

CLINICAL CENTER

CLINICAL CENTER

Especially designed as a research facility, the NIH Clinical Center is 14 stories high, with 516-bed patient areas and 1,100 laboratory modules in close proximity. Its primary purpose is to promote the physical and mental well-being, and when possible, the restoration to health of patients under study by the various institutes.

The Center provides professional and related services through two branches--Administrative and Employee Health--and through the following departments: Anesthesiology, Blood Bank, Clinical Pathology, Diagnostic Radiology, Environmental Sanitation Control, Medical Records, Nuclear Medicine, Nursing, Nutrition, Pathologic Anatomy, Pharmacy, Rehabilitation, Social Work, and Spiritual Ministry.

Patient Care

To assure patient care of the highest quality, medical specialists from many disciplines and representing many institutes are centered within the one building, available for focusing attention on the problems of the patient. The staff emphasizes warm, personal care as well as efficient professional treatment.

Eight of the institutes and the National Institute of Mental Health are allotted bed space. The institutes select patients--referred to NIH by physicians throughout the United States and other countries--for current clinical studies of specific diseases and disorders. About 15 percent of the patients are "normal volunteers"--healthy persons who provide scientists with an index of normal body functions against which to measure the abnormal. Normal volunteers come under such varied sponsorship as colleges, civic organizations, and religious groups.

Research

With the exception of direct physician care, all patient services are provided by the Clinical Center. The names of the departments are indicative of their functions. Professional staff members of these departments serve on the research team. The Nursing Department is illustrative: nurses assume a responsible role in the National Cancer Institute's chemotherapy programs, in the National Institute of Neurological Disease and Stroke's studies of the mentally retarded child, and in the National Heart and Lung Institute's program for continuous intensive care of patients who have undergone heart surgery.

Staff members of many of the departments also conduct research leading to progress in their own specialties. Examples are the Clinical Pathology Department's study of hematological and chemical profiles in normal individuals; the Blood Bank Department's study of the serologic relationships between various blood constituents and disease states; the Rehabilitation Department's evaluation of the use of plaster casts and splints in the treatment of patients with rheumatoid arthritis; the Pharmacy Department's continuing formulation of suitable dosage forms for clinical investigative drugs along with the development of quality control procedures, stability studies, and drug registration; the Anesthesiology Department's long-range study of the physiological changes that occur during the use of various types of general anesthesia for ambulatory patients undergoing multiple dental extractions, and its cooperation in a national study to evaluate the possible hepatotoxic effects of various anesthetics, including halothane.

Professional Training

The Clinical Center assists the medical and scientific staffs of the institutes administratively and procedurally by conducting a program for appointment of young physicians to Associateships and provides assistance in residency training and related programs. In addition, the Clinical Center provides advanced training for Clinical Associates in the Anesthesiology, Diagnostic Radiology, Nuclear Medicine, and Blood Bank Departments. The Associates serve as researchers for two to three years under the guidance of senior staff members. The Clinical Pathology and Pathological Anatomy Departments offer fully approved residency programs. Nuclear Medicine has approval for two years of residency training.

The Clinical Center coordinates a clinical electives program, established in 1970, open to students from any of the Nation's medical schools. These electives emphasize the investigative approach to medical problems. The students rotate through the various clinical wards and also participate in special rounds and conferences.

Four times a year the Nursing Department of the Clinical Center conducts a similar program of elective courses open to students from any of the Nation's baccalaureate programs in nursing. The program consists of courses related to the speciality practice area coordinated with planned practice directed toward established goals, and is designed to provide an in-depth exposure to a nursing speciality in a research environment.

From September to June each year, the Education Committee of the Medical Board sponsors a series of Combined Clinical Staff Conferences and a similar schedule of general medical grand rounds. The proceedings of at least six clinical staff conferences are published each year in the Annuals of Internal Medicine.

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Mission

The programs of the Division of Computer Research and Technology (DCRT) are directed first toward processing the wealth of information generated by the scientific research which defines the NIH mission. In addition the DCRT provides administrative data processing services and policy analysis. Finally, the Division conducts its own research program in computer science, mathematics, and physical science.

DCRT Services and Facilities

DCRT services and facilities are designed to automatically process research data and other data that are the basis for administrative action:

- DCRT operates the NIH computer center on a business basis. It emphasizes flexible configuration and easily accessible services to meet the needs of NIH scientists and managers.
- It maintains a staff of computer systems analysts and programmers as well as mathematicians, engineers, and life scientists as a central resource to meet the wide variety of NIH needs and to collaborate with NIH scientists on biomedical problems amenable to computer solution.
- It educates the NIH staff by means of a comprehensive series of computer courses so that they may make independent and informed use of the available facilities and resources.
- Over all, it relies on a concept of distributed computational capacity with large centrally located machines available as a computing utility, smaller computers strategically located around campus for specific communities of users with their particular needs, and smaller custom-designed machines dedicated to single applications. These communicate with one another by a variety of means, usually ordinary telephone lines.

Research and Development

To support delivery of these services and insure that computers achieve their greatest effective potential in relation to biomedical science, DCRT carries on research and development. Research programs in computer science, engineering of software and hardware, mathematics mathematical statistics and physical science make available the best techniques for application in the biomedical programs of the institutes.

Organization

DCRT is organized along functional lines with six laboratories and branches having complementary disciplines and areas of expertise (see Figure 1). The range of concern extends from computers themselves to theoretical chemistry and physics.

Computer Systems

The DCRT biomedical computing facility is the world's largest. The Computer Center Branch currently processes about 5,000 jobs a day, with four large computers acting in concert in one configuration and two in another. Each is accessible from the several hundred remote terminals at NIH, and each in turn can gain access to central on-line files, containing "shared libraries" of computer programs and data sets. Any one of the machines is, therefore, able to process the next waiting job, since all are equally capable of calling the suitable program and data.

The center serves more than 4,000 registered users, primarily at NIH, with the remainder at certain other Federal agencies engaged in health-related research. Since the mature and knowledgeable computer user is of primary concern to the division, peripheral equipment and software have been designed to his needs. He may use a terminal located close to his laboratory or office to communicate with the computers. Resident computer programs such as WYLBUR and TSO allow him directly to edit text, create files, and manipulate his data. Several graphics devices enable him to "model" his data, to display three-dimensional structures, or to draw a molecule. When appropriate and feasible, the DCRT staff of engineers can custom-design a computer system for him as well as the specialized interfacing hardware that he may need.

Application Programming

Some of the jobs processed are administrative and use the DCRT machines for data processing only. This is true of the jobs from the Division of Research Grants, the Office of Financial Management, and the NIH Personnel System. DCRT analysts and programmers work on the new needs of NIH staff, including large biomedical data systems such as a cholesterol level project--the Type II Coronary Intervention Study--at the National Heart and Lung Institute and the National Cancer Institute's Carcinogenesis Bioassay Data System. The research and management needs depend on sophisticated data-management systems and a highly trained staff.

Biomedical Problems and Advanced Computer Technology

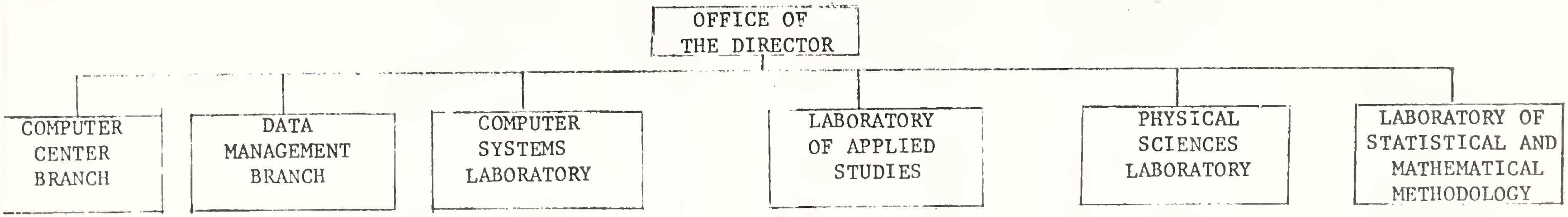
DCRT laboratories are concerned primarily with research and development in computer technology as it relates to the biomedical environment. Laboratory staff represent a large number of scientific disciplines from medicine itself to theoretical physics and often collaborate with or act as consultants to scientists from other institutes. The problems dealt with may range from the automatic

Figure 1.

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

MISSION: Provision of essential services and conduct of research and development for support of NIH mission in modern biomedicine.

ORGANIZATION:


OFFICE OF THE DIRECTOR
COMPUTER CENTER BRANCH
DATA MANAGEMENT BRANCH
COMPUTER SYSTEMS LABORATORY
LABORATORY OF APPLIED STUDIES
PHYSICAL SCIENCES LABORATORY
LABORATORY OF STATISTICAL AND MATHEMATICAL METHODOLOGY

OUTPUTS:	- modern computer facilities and services	- tailored computer programs/ systems	- adaptive scientific computer systems	- mathematical solutions and methods for:		
				- biology and medicine	- biophysical science	- statistical analysis
MODES:	- "systems" programming - operations - facilities training	- general purpose programs - systems analyses, design, development and training	- instrumentation	- analysis: mathematical statistics	- kinetic analysis - thermodynamic analysis	- numerical analysis
DOMINANT SUBJECT AREAS:	- systems engineering	- information systems analysis & design	- electronic engineering	- biology & medicine	- chemistry physics	- interactive man-computer problem solving

BASIC DISCIPLINES:

.... computer science .... engineering .... applied mathematics ....

capture, analysis and display of data from laboratory instruments to the automatic evaluation of the electrocardiogram and generally require mathematical or engineering expertise for solution. In addition, such natural phenomena as the electrostatic forces acting between cells and the cells' active transport mechanism have been examined by division physicists and chemists.

Research on Computational Methods

As a scientific research institution, NIH is in the business of collecting data, evaluating them, and analyzing them statistically, to obtain information that will aid in the treatment and cure of disease. Scientific data are voluminous, and research on methods of handling them efficiently and economically is one of the division's responsibilities. Another project, in computational linguistics, is concerned with automatically encoding or indexing medical statements in English and other languages and arranging this information in such a way that it is easily retrievable.

On-line computer-aided modeling supports science by enabling a researcher to use a computer terminal and cathode-ray tube to compare experimental with expected results, and to try again in the event of a discrepancy, changing various parameters in his equation. Manipulation of chemical structures, using computer display, aids in the study of such things as the chemical bond or the nature of the chemical molecule. All these techniques help the scientist by reducing his data to manageable proportions and doing some of his tedious, time-consuming analysis.

Information and Education

Technical reports resulting from Division research programs are published for general use, as are technical and self-teaching manuals. A research library houses 150 journals and many of the important monographs in computer and information science.

The research program keeps DCRT staff abreast of current developments in computer technology and they communicate this knowledge to users by teaching courses in programming languages, special-purpose computing facilities, and selected areas in computer science, applied mathematics, and engineering. From time to time the Division undertakes intensive educational programs designed for special groups of students.

FOGARTY INTERNATIONAL CENTER

FOGARTY INTERNATIONAL CENTER

The Fogarty International Center for Advanced Study in the Health Sciences is designed to advance man's knowledge in the biomedical and allied sciences, and to relate new knowledge to present-day society. It fosters international cooperation and collaboration in the interests of the health of mankind and, as the first center for advanced study within the Federal structure, may develop major intellectual undertakings unrestricted by jurisdictional considerations. Through exploration of such undertakings in the Center, ideas and syntheses having impact upon the future development of medical and biological sciences and the nature of health action in the future can emerge.

Because of the strong interactions between the programs of the Center and the interests and responsibilities of other units of the National Institutes of Health, as well as U.S. universities and other Federal agencies, the Center's efforts are coordinated with these organizations, and are intended to complement and strengthen existing capabilities of others through cooperative effort.

Advanced Study

The Center's programs of advanced study rest on the premise that research has made great progress in responding to the needs of society, its environment, and the growth of individuals. If this progress is to continue, however, it must be based upon a broader and better informed community. The informed citizen of the future cannot be indifferent to the impact of science on his life. At the same time, the biomedical community must be more sensitive to the spirit of the times. Among the areas currently being studied at the Center are such problems as the state of the art of preventive medicine and public health as practiced in the United States and in the USSR and the People's Republic of China, and of medical education and training.

Preventive medicine is being studied on the assumption that improvement in the health status of the American people will be dependent in great measure on the design and application of programs which place major emphasis on the preventive aspects of human disease problems. Although most agree with this thesis, there is a need for more precise definition of effective methods or programs for prevention, of financial resources required to implement these programs, and of priorities to be assigned to research in preventive methodology.

Conferences on preventive medicine, already held or planned for the 1972-1975 period, are considering the state of the preventive art in oral health, obesity, diabetes, diseases of fetal development, and infectious diseases.

Special efforts will be made to identify those aspects of clinical trial and basic preventive medicine research which are most likely to be productive in the foreseeable future. Additional categorical reviews are contemplated as well as study of health maintenance methods and the economic impact of deranged health and of programs of prevention. Emphasis is also being placed on current concepts of lifestyle modification, health promotion, and new delivery systems.

The Center is studying medical education and training because biomedical research and medical education are inextricably linked and mutually dependent for continued advancement and vitality. Virtually all countries share common problems and goals in educating and training future leaders for the achievement of high standards of health care. Differences in approach to that goal are more a reflection of differences of cultural, social and economic characteristics than of purpose. Sharing ideas and experiences can be mutually beneficial.

Action taken by the Center in coming years will be designed to accumulate and maintain information about current and changing patterns of medical education in advanced and developing countries, to evaluate such information with respect to health-care problems, and to initiate, support or assist the development of individual or collaborative studies, or of programs pertinent to these purposes.

In addition to the interests mentioned above, the Center is continuing to study problems in fundamental science, to achieve a greater understanding of biological and behavioral sciences through advanced study, and to identify the legal, ethical, social and economic problems that may arise from new findings of biomedical research. To date, the Center has sponsored over 30 conferences, workshops and symposia, involving hundreds of international specialists in such fields as human genetics, population and family planning, and environmental health problems. Approximately thirty publications have resulted from these conferences.

Geographic Studies

Within the geographic studies program, the Center is undertaking continuing studies of medicine and public health in the USSR and the People's Republic of China.

Over the past 14 years, a number of U.S. missions have traveled to the Soviet Union to explore the role and accomplishments of medicine, public health, and research in the USSR. To maximize the productivity of such exchanges -- recently expanded by a new agreement on cultural and scientific exchanges -- the Center has issued a series of studies on Soviet medicine and public health. In the future this series will include the development of study projects and publications in the fields of heart, cancer, and environmental health, as well as articles, bibliographies, and monographs on medicine and public health.

The Center's interest in the People's Republic of China became active over two years ago. Since then, a handbook on the current status of medicine and public health in the People's Republic has been issued and a number of studies of Chinese medicine initiated. Currently the Center is providing leadership in collecting, analyzing and publishing data essential to the development of effective cooperation between the United States and the People's Republic of China.

Fellowships and Scholars

The Center's interest in promoting the exchange of ideas among working scientists has been reflected in (a) the long-term support of an International Research Fellowship Program, (b) the recent establishment of a Senior International Fellowship Program which will enable U.S. scientists to become involved in scientific activities outside the United States, and (c) the Scholars-in-Residence Program.

(a) The International Research Fellowship Program was initiated in 1958 primarily to encourage the development of a collaborative relationship between U.S. laboratories and promising young foreign biomedical scientists in attacking problems of common interest. This involves cooperation with 40 participating countries, each responsible for screening and recommending its applicants to the Center. Successful nominees obtain advanced research training and participate in collaborative research in a number of educational and research institutions throughout the United States including the National Institutes of Health. The U.S. scientific community profits considerably from the presence of these promising young scientists who work closely with U.S. scientists in the laboratory. During the 15 years that the program has been functional, a number of meaningful contributions have been made by each of these fellows, and the value of their presence in U.S. laboratories has been pointed out by many senior staff in the universities. Basing the choice of fellows on the merit principle has made it possible to maintain relatively high standards, thereby insuring that expenditures support only the best available people. Thus far, the program has involved more than 1400 participants representing 40 countries throughout the world.

(b) During the current fiscal year (1974-75), the Senior International Fellowship Program will be initiated to provide an opportunity to U.S. scientists in mid-career (each nominated by his/her university) for participation in programs outside the United States. In the early phases of this undertaking, participation will be limited to faculty members of Schools of Osteopathy, Dentistry, Medicine and Public Health. Participants are expected to profit considerably from overseas experience; in particular, they will be expected to make a significant contribution to their parent institution as a result of this experience.

(c) The Scholars-in-Residence Program, unique as well as crucial to the success of the Center's overall program responsibilities, provides an opportunity for convening outstanding authorities from the United States and foreign countries to direct their attention to the pursuit of problems within their own discipline as well as related fields of interest. While Scholars-in-Residence, these individuals are removed from day-to-day incursions upon their time and energies and are provided with the necessary logistic support to enable them to give full attention to important broad problems in science and to the application and consequences of scientific advance upon modern society. The Scholars relate very broadly to virtually all programs within the NIH and as a group have provided a meaningful intellectual stimulation within the biomedical community. This program is by invitation only and has attracted highly qualified persons from countries throughout the world.

Gorgas Memorial Laboratory

The Gorgas Memorial Laboratory, located in the Republic of Panama and supported in part by a contribution from the U.S. Government, is administered by the Fogarty International Center. The current program results from merger of the Gorgas Memorial Laboratory and the Middle America Research Unit. This merger assures the potential for development of a unique medical research and education program in international health. New legislative authority has been proposed for this and is anticipated that the Fogarty International Center will play a major role in the reorganization of the Gorgas Memorial Laboratory program to insure its harmony with biomedical research interests of the Federal Government in the Western Hemisphere.

Support Functions

In addition to its own programs the Fogarty International Center provides administrative support to several vital international activities.

Special Foreign Currency Program

Biomedical research and health science information exchange activities are carried on in selected countries abroad through the Special Foreign Currency (PL 480) Program administered by the Center. The program is funded with U.S.-owned foreign currency and does not require dollars from tax revenues. All projects are collaborative, bringing the efforts of scientists both in the U.S. and abroad to bear on problems of mutual interest. Projects are subject to review within the host country for technical merit and conformance with national health science priorities. In the seven participating countries -- Egypt, India, Israel, Pakistan, Poland, Tunisia, and Yugoslavia -- there are 131 projects with an annual expenditure of approximately $4.4 million equivalent.

International Education Program

Programs are arranged throughout the United States for the training of approximately 550 medical and allied health personnel from some 85 countries annually. These professional health workers are financially supported by the World Health Organization and other United Nations agencies. The Center also provides the administrative functions for the selection of United States candidates for WHO fellowships abroad in the interest of improving this country's health services. Approximately 50 scientists from local governmental agencies and educational institutions are involved annually in the study of health services and activities in various countries throughout the world.

International Visitors Center

To facilitate the flow of technical information, hundreds of foreign scientists are welcomed each year at the National Institutes of Health. The International Visitors Center within the Fogarty Center is the focal point for guidance and assistance to these visiting scientists. The visitors' center also administers the NIH Visiting Program which since its beginning in 1950 has provided an opportunity for 1955 qualified foreign scientists to train and work with NIH scientists. There are at present about 350 scientists participating in this program for continuing exchange of biomedical knowledge.

Finally, the Fogarty International Center, despite its short history, provides leadership in the sensitive area of ensuring that NIH activities conform to international policies and procedures, since it is increasingly apparent that the activities of NIH affect the foreign policies of this Government.

DIVISION OF RESEARCH GRANTS

THE DIVISION OF RESEARCH GRANTS

Functions

The Division of Research Grants (DRG) is broadly responsible for providing staff support to the Office of the NIH Director in the formulation of grant and award policies and procedures, receipt and referral of applications for research and training support, scientific review of certain types of applications, the analysis and evaluation of management and program data needed in the administration of extramural programs, administration of the DHEW policies for protection of human subjects and animals used in research, and administration of the Grants Associates Program. Following is a brief functional statement for each of the branches.

Referral Branch

All applications to the Public Health Service/DHEW requesting support for research and research training activities are received in the DRG Referral Branch. They are then referred either within the National Institutes of Health or routed to one of the five other health-oriented agencies of the Public Health Service. Those applications assigned to NIH are further assigned to one of the awarding components (institutes) of NIH for program review; the majority of these are also assigned for scientific review to an initial review group (study section) within DRG.

The Referral Branch develops and publishes the criteria for determining appropriate assignment of applications within the NIH by program area and by the competence of the respective review groups.

Scientific Review Branch

The Scientific Review Branch administers the DRG initial review groups or study sections which provide scientific and technical advice on applications for research and research training support. The number of study sections has varied over the years depending on the volume of applications to be reviewed and the changing nature of research. In July 1974, there were 47 sections. These have been augmented from time to time by ad hoc groups who review applications in special areas not covered by the regular sections.

A study section is made up of outstanding research scientists in its special field. Members review each application assigned to the group and make recommendations to the national advisory council of the institute with program responsibility for the application.

The Scientific Review Branch also stimulates and coordinates study section surveys of research fields undertaken to determine the current status of research and to identify needs for further development.

The Office of Research Manpower

The Office of Research Manpower is a focal point at NIH for the coordination of the several types of research fellowships, training grants, National Research Service Awards, and career development awards. The office provides support for policy direction by the Office of the Director and coordination for the planning and development of the research manpower mission of NIH. It advises and assists awarding units in developing new programs.

The office interprets administrative policies and procedures governing NIH research manpower programs and serves as liaison with grantee institutions to provide technical assistance in their implementation. It has also conducted studies of the various types of research training programs, in cooperation with other appropriate organizations, to identify national needs for research and academic personnel in the health-related sciences, and represented NIH on interagency groups regarding Federal standards for training support.

Statistics and Analysis Branch

The Statistics and Analysis Branch is the NIH central source of statistical and management information for the administration of the extramural programs. It operates two large central information data systems--IMPAC* and CRISP**--for recording, compiling, and reporting operating and statistical data on the extramural programs. These data are used to meet the reporting requirements of NIH, to provide information on the scientific and administrative characteristics of the grants, contracts, and awards processed through the system, and to respond to inquiries from other Federal agencies, the Congress, the scientific community, and the general public.

Research Analysis and Evaluation Branch

The Research Analysis and Evaluation Branch is the principal NIH staff resource in the development and preparation of reports on those aspects of selected biomedical fields that are of interest to NIH in planning and decision making in the administration of extramural programs. For example, the branch provides a continuing analysis of the scientific content of biomedical research fields supported by NIH extramural programs and it studies the trends in the types of support being requested and the sources of support. Branch reports are used by NIH management and program analysis officers, the Secretary of DHEW, the National Academy of Sciences, the Congress, and the scientific community.

* Information for Management, Planning, Analysis, and Coordination

**Computer Retrieval of Information on Scientific Projects

Institutional Relations Branch

The Institutional Relations Branch acts as technical liaison with grantee institutions in the interpretation and implementation of nonfiscal policies and procedures related to extramural programs in general. The branch acts for all components of DHEW in administering the Department's policy on protection of human subjects and in negotiating grantee assurances of compliance with the policy.

A classification system has been developed for projects identified by scientific review groups as involving ethical problems or potentially hazardous procedures. The branch follows up on these to insure that any criticism of projects approved by grantee institions is conveyed to institutional review groups.

The branch also negotiates assurances of grantee institution compliance with DHEW policy on care and treatment of laboratory animals.

DIVISION OF RESEARCH RESOURCES

DIVISION OF RESEARCH RESOURCES

The Division of Research Resources (DRR) is the component of the National Institutes of Health which has the responsibility for the initiation, development, and support of noncategorical resources needed on an institutional, regional, or national basis for highly sophisticated health-related research. Resources that conform to this definition are those which, because of their cost, complexity, or expected life, can be justified only if they serve multiple and varied projects, and require support over an extended period of time. They are supported by DRR under five broad-based programs--Clinical Research Centers, Biotechnology Resources, Laboratory Animal Sciences and Primate Research, General Research Support, and Minority Biomedical Support. Located at academic and research institutions, these resources provide the underlying support--the tools, environment, and continuity of funding--necessary for the targeted and fundamental research missions of the NIH. And by promoting and fostering interdisciplinary and multidisciplinary research endeavors they increase biomedical research productivity and opportunity.

General Clinical Research Centers Program

The goal of the General Clinical Research Centers Program is to provide clinical investigators in widely scattered geographic locations with specialized resources and facilities necessary for the conduct of clinical research. Since these Centers are multicategorical, research conducted there benefits from the interaction of investigators who share their experience and expertise in a range of clinical research areas in designing, conducting, and interpreting investigations.

Traditionally, support has been provided for a fixed number of hospital beds in a discrete area chiefly within university-affiliated hospitals staffed by specialized nursing, dietary, and laboratory personnel. Over the years, in response to the changing needs of clinical investigators, the concept of a center as a geographically and physically discrete inpatient unit has been extended beyond the research limitations of a solely inpatient unit to include facilities and personnel necessary for an outpatient or ambulatory clinical research program. The use of outpatients in clinical research provides opportunities which are not possible in purely inpatient studies and are particularly important in the areas of genetics; epidemiological surveys and analyses; and in studies of chronic exposure to such agents as asbestos, lead, or radiation.

Biotechnology Resources Program

The Biotechnology Resources Program provides life scientists with the access to highly specialized instruments, methodologies, and expert supporting staff required for maximum exploitation of new and advanced technologies. Development of new knowledge through health research is subject to numerous constraints. Prominent among these is technological limitation. Critical research questions can be asked that either cannot be answered with existing technological capability or that require effort of such magnitude and duration that their solution is not attempted. In other cases, existing technology lacks necessary precision and conclusions based on it are tenuous. To reduce such constraints the Biotechnology Resources Program has established an enriching interplay between biology and medicine on the one hand, and the physical sciences, mathematics, and engineering on the other, primarily through the emphasis on digital computation, mass spectrometry, nuclear magnetic resonance spectrometry, and electron microscopy.

Advances in supportive technologies promise to make computer resources more effective in meeting health research needs. In the near future, for example, refinements in inter-computer communications techniques will allow specialized resources to serve users throughout broad geographical areas. They will also permit flexible access to a variety of computers and data bases from a single terminal, allowing redundancy reliability, and therefore allowing introduction of computers into reliability-critical components of research (such as clinical research). In the longer run, deeper understanding of the structure of research and clinical information, coupled with advances in goal-directed computer programs, will greatly increase the usefulness of health information data bases, both for the individual biomedical investigator and as shared by an entire research discipline.

Mass spectrometry and nuclear magnetic resonance spectrometry offer biomedical scientists a powerful technological tool for the characterization of molecular structure. These techniques have been applied widely for the study of biologically related synthetic chemicals, natural products, and the constituents of body fluids.

Laboratory Animal Sciences Program

The Laboratory Animal Sciences Program assists institutions in providing the animal resources vital to biomedical research. The major dependence of health research on the use of animals emphasizes the need for quality animals to be available to a large number of research investigators under conditions which minimize costs and procurement time. The Program is meeting this need through grant support with the specific objectives of:

1. developing and maintaining laboratories for the diagnosis and investigation of naturally occurring diseases of laboratory animals;

2. providing new knowledge regarding laboratory animal diseases and optimal husbandry of laboratory animals;

3. defining and elucidating new animal biological models;

4. developing and maintaining colonies of special research animals; and

5. gathering and disseminating information regarding laboratory animals.

Primate Research Centers Program

The Primate Research Centers Program is a national focus for the use of subhuman primates, the animal species biologically closest to man. For this reason, they are the animals of choice for many studies of human health and disease, in some cases the only suitable species.

Subhuman primates are difficult to breed, and are expensive to buy and to maintain. Specimens from the wild carry both apparent and unsuspected simian diseases and are susceptible to devastation by human diseases for which they lack natural or acquired immunity. Moreover, the supply of subhuman primates from the wild is limited and is becoming constricted at a time when demand is increasing and domestic breeding capability is woefully inadequate.

The Primate Research Centers Program addresses these problems by: (1) rendering animals from the wild suitable for health research; (2) developing the science of primatology the better to deal with problems of care, disease prevention, diagnosis and treatment, and breeding; (3) providing an environment for primate research that could not be achieved or could be achieved only with difficulty elsewhere; (4) developing primate models of diseases and conditions; and (5) offering training and expertise in primatology which makes multidisciplinary research possible and reduces costs of research in primates by helping investigators to avoid costly mistakes in selection and care of primates, and in the design and conduct of experiments in these species.

General Research Support Program

The General Research Support Program provides flexible institutional funds on a formula basis to health professional schools, non-Federal hospitals, municipal health agencies, other nonprofit, non-academic research organizations, and components of academic institutions other than health professional schools actively engaged in biomedical research. These funds are complementary to categorical project forms of biomedical research support. The most distinguishing feature of this program is that it provides the grantee institution an opportunity for exercising on-site judgment in decisions on emphasis, specific direction, and content of activities supported, thus enabling it to respond quickly and effectively to emerging opportunities and unpredictable emergencies, to enhance creativity, to encourage innovation, to provide for pilot studies, and to improve research resources, both physical and human.

Minority Biomedical Support Program

The Minority Biomedical Support Program provides funds on a competitive basis to assist minority institutions (black, American Indian, Spanish-speaking, and Polynesian) to build up a biomedical research and research training capability. The Program serves to increase the numbers and broaden the opportunities for research and/or research participation of ethnic minority faculty, students, and investigators in the biomedical sciences.

DIVISION OF RESEARCH SERVICES

DIVISION OF RESEARCH SERVICES

Programs

The Division of Research Services (DRS) supports other components of the National Institutes of Health by providing centralized and collaborative scientific, engineering and technical support essential to biomedical research. The Division provides consultation, products, and services through programs in biomedical engineering and instrumentation, environmental health and safety, library sciences, medical arts and photography, veterinary medicine and animal sciences.

Production Figures

Last year the Division produced and issued 119,000 liters of high quality microbiologic media, 546,000 mice, rats, hamsters, guinea pigs, and rabbits, and over 4,000 nonhuman primates, ungulates, dogs, and cats. More than 3,700 instrument fabrication projects were completed and 8,200 systems maintenance jobs were carried out. DRS also processed and issued 9,000,000 pieces of glassware, loaned 32,000 books and journals, produced 180,000 photographs, and made 6,300 statistical charts and technical drawings. This is a sampling of the diversity of end products supplied by DRS.

Professional Services

Equally important, though less tangible, were the expert advice and consultation provided to research scientists by DRS biomedical engineers, veterinarians, animal geneticists and nutritionists, library service advisers, translators, visual communication advisers, environmental engineers, health physicists, safety specialists, sanitarians, and microbiologists.

Animal Resources

A Division genetic repository for the development, maintenance, and distribution of animal models of human disease serves the international biomedical research community. Breeding nuclei of the special strains in this repository are made available to other research institutions throughout the world. Currently more than 130 characterized strains and stocks of rodents are maintained and catalogued in the repository. New strains with significant research potential are periodically added.

Animal disease investigation, diagnosis, and control services are used extensively by the NIH intramural community and are important in protecting the health of the approximately 400,000 animals housed by NIH on its Bethesda campus.

The Division also maintains facilities and resources for experimental surgery in which approximately 650 surgical procedures are carried out annually. A new innovation is a canine blood donor colony which has dramatically reduced the need for sacrificing animals during surgical procedures which have direct application to human surgery, particularly in heart and lung technology. In addition to canine blood, other biologic materials provided by the Division include sheep red blood cells, equine sera, tissue culture, and cell lines.

Biomedical Engineering and Instrumentation

The Division creates highly specialized, otherwise unavailable, laboratory instruments and provides biomedical engineering knowledge and technical skills required to implement research and applied projects of the National Institutes of Health. Operations include a repair and preventive maintenance program for scientific apparatus; a comprehensive scientific equipment loan program, which is available to NIH researchers to conserve equipment and funds; and satellite engineering support personnel and facilities located in or near research areas where immediate needs are acute.

Recently, DRS demonstrated the utility and effectiveness of other new concepts and techniques by establishing mathematically derived chemotherapeutic protocols and applying pharmacodynamic principles to achieve more optimal hemodialysis. Clinical instrumentation systems based on video technology were accepted for monitoring cardiac performance and the condition of the aortic ball valve prosthesis *in vivo*. Division personnel have also significantly improved noninvasive ultrasonic imaging for heart structures.

DRS has initiated investigations in other important areas, including the identification and assessment of trace metallic complexes in cancer therapy and environmental contamination; the interaction of implanted polymers with blood and body fluids; and fluid mechanical influences on atherosclerotic plaque formations.

Environmental Health and Safety

An integrated research-oriented environmental health and safety program, under the leadership of the Division of Research Services, includes illness and accident surveillance with epidemiologic investigations; radiation safety, and physical, chemical, biological, and industrial safety. The program monitors and protects the scientists and their supporting staffs, as well as protecting the integrity of the NIH research environment. It is designed to identify, solve, and prevent environmental problems. The Division trains technicians and updates information for investigators in safe practices and procedures for achieving the environmental control essential to scientific experimentation.

Library Services

The Division provides convenient facilities and resources for study and reference work. Its reference services and collection of books and journals are directly related to current research programs and is a resource matched by few medical libraries. Specifically trained professional advisers are available for consultation, and trained analysts formulate requests for services provided by computer reference retrieval systems.

Medical Arts and Photography

Services such as photomicrography, motion picture production, gross specimen photography, and general photography are provided the NIH. Research results are communicated through media developed by skilled professionals and technicians with expertise in such areas as medical modeling, medical illustrations, statistical tables and charts, technical drawings, general illustrations, and computer-based graphics. Producers, artists, illustrators, and designers counsel researchers on visual material.

Outlook

An increase in the number of individual research projects and collaborative efforts with bench scientists and administrators is expected. The direction of the DRS programs is clearly related to changes in emphasis experienced by other segments of the NIH. The prime Division objective is to continue to maintain and develop essential resources at a level which will continue to make NIH a uniquely equipped place in which to conduct modern sophisticated biomedical research.

CONTRIBUTIONS
FROM
NATIONAL INSTITUTES OF HEALTH, U.S.A.

Informal Meeting on Collaboration Between Medical Research Councils
and the World Health Organization
Geneva, December 2-4, 1974

National Institutes of Health
December 1974

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